

\* Create strategies & action plans to accelerate the integration of personalized health care into clinical practice & health care delivery

\* Develop effective strategies to capitalize on the disruptive innovation characteristics of personalized health care

\* Identify methods & incentives that enable providers to optimize outcomes on both an individual basis & population basis

# Personalized Health Care: Pioneers, Partnerships, Progress

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*Personalized health information...*

*Based on individual biology...*

*Yielding precise and predictive health care.*

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**November 2008**



**Personalized Health Care**  
**Pioneers, Partnerships, Progress**

*U.S. Department of Health and Human Services*  
*November 2008*



## ***ABOUT THIS REPORT***

This is the second report prepared by the Initiative on Personalized Health Care, located in the Office of the Assistant Secretary for Planning and Evaluation in the U.S. Department of Health and Human Services. The Initiative was undertaken as a priority of HHS Secretary Michael O. Leavitt.

An earlier report, *Personalized Health Care: Opportunities, Pathways, Resources*, was released in September 2007 and focused especially on federal activities. It included summaries of federal efforts in the areas of expanding the science base for personalized health care; supporting health information technology; regulatory responsibilities; implementing personalized medical products and services in clinical practice; and ethical, legal and social issues. Some 50 programmatic areas were inventoried.

In this year's report, the Initiative seeks to bring into focus a sampling of activities that are now underway in different parts of the private and academic health care sectors toward integrating personalized health care into clinical practice. This includes efforts to employ genomics and other molecular level techniques in clinical care; the use of health information technology in care, including the integration of clinical care with research goals; and the realignment of traditional organizations toward enhanced individualization of treatment and patient-centric approaches.

The Initiative commissioned seven papers, examining the challenges and opportunities of personalized health care from the perspective of different stakeholder elements in the health care sector. These perspectives range from the integrated health delivery organizations and academic medical centers to medical professional societies, venture capital firms, and patient advocacy organizations.

The Initiative also invited several leading "communities" (medical institutions and their partners) to contribute reports of their activities and plans toward different aspects of personalized health care. Ten community case studies in this report help illustrate how personalized health care is coming to be defined, designed and delivered at the leading edge.

In October, the commissioned papers and community case studies were shared with participants of the National Summit on Personalized Health Care in Deer Valley, Utah. The Summit brought together leaders in the personalized health care field to identify barriers and strategies for progress. A summary of proceedings and outcomes of the Summit is also included in this report.

The commissioned papers and community case studies included in this report are intended to help illustrate the scope, status and goals of personalized health care. They represent the views and experience of the authors, and are not intended to represent the opinions or policies of the U.S. Department of Health and Human Services.



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# Prologue





# **PROLOGUE**

**By Michael O. Leavitt**  
**Secretary of Health and Human Services**

We often tell ourselves that we live in an age of “medical miracles.” So it might seem heretical to suggest that in the not-too-distant future, people could be looking back and concluding that medical care in 2008 was still in a relatively primitive state. And yet the case can be made.

Not that we’re in the time of the shamans. We look to science, technology and proof – not magic – for the tools of medicine. Yet even with our strong science base, it is only in recent decades that we’ve noticed how haphazardly we use that base. The work of John Wennberg and others, beginning in the 1970s, has shown how much variation exists from region to region in standards of medical practice, as well as the outcomes and costs of care. Hence the emphasis today on “evidence-based care” – the need for a process that identifies which treatments work most effectively for which conditions. The quest for evidence-based care is a worthy one. But it also illustrates how far we remain from a well-organized system that delivers the best care to each patient.

Even more than that: We are at an early stage in our ability to differentiate between variations in the biology of individual patients and provide effective treatment for different diseases. We have developed powerful pharmaceuticals – yet most drugs prescribed in the United States today are effective in fewer than 60 percent of treated patients. This efficacy rate reflects the variability of metabolism or other factors from person to person. One study has found that prescribed drugs are ineffective or less effective for at least 70 percent of those who take ACE inhibitors and beta-blockers, for nearly 40 percent of those prescribed antidepressants, and for at least 30 percent of those prescribed statins for high blood pressure or given beta2 agonists for asthma. It remains common medical practice to follow a trial-and-error process for finding the right diagnosis, the right treatment and the right pharmaceutical dosage for each patient.

Even our definitions of diseases remain rooted in 18<sup>th</sup> and 19<sup>th</sup> century terms. We refer to asthma, but there are many varieties of asthma. From a treatment perspective, they are actually different diseases, yet we are barely at the cusp of being able to identify them accurately and provide the right treatment at the first encounter. We refer to colon cancer, but this term is really a surrogate for five different known diseases. We refer to breast cancer, but in reality there is no such single disease – rather, cancers of different kinds may arise in breast tissue. From a treatment perspective, the notion of treating “breast cancer,” as opposed to a cancer that arises from dysfunction in a particular gene-based mechanism, is already outdated. One result is that most women who are treated with dangerous, painful and expensive chemotherapies are receiving treatments that are actually ineffective for their condition.

On the other side of the ledger is our opportunity for increased medical effectiveness through the ability to differentiate diseases more accurately – to the point of redefining disease. In the case

of blood cancers, the only available diagnoses some 80 years ago were leukemia and lymphoma. By 1950, three forms of leukemia and two kinds of lymphoma had been identified. Today, we have identified 38 types of leukemia and 51 types of lymphoma. These distinctions have helped steer drug development such that treatment can often be highly personalized and survival rates for many of the subtypes have gone from virtually zero to as high as 90 percent.

And then there is the state of information in health care. In a time when information technology has transformed most other sectors, with particular benefit to the consumer, the health care sector, with its paper files, often inaccessible records, and incomplete patient data, stands out as primitive indeed.

These constitute serious limitations on our ability to deliver the right care to the right patient at the right time. However, with the completion of the Human Genome Project and the subsequent torrent of new biological discoveries at the molecular level, we foresee the possibility that a new door may open in medical care. As our knowledge in these areas increases, we should acquire a new, clearer, more precise and increasingly actionable view of human health and disease. At the same time, modern information technology can be used to support physicians and consumers alike in improving health care and health maintenance.

In the coming years, we will strengthen our evidence base for health care, and we will find new ways to help providers deliver the best standard of evidence-based care. We will also be moving rapidly toward a new, molecular-based understanding of health and disease. Over time, these two vectors will meet. In that way, we will develop not only the tools to help providers deliver the care that works best “on average,” but at the same time we will develop a new class of tools for identifying and employing the best care for each *individual* patient.

This is the goal called “personalized health care.” In some ways, there is nothing new about the goal of personalizing health care. It has always been the intention of the health professions to deliver personalized care, and we rely on the experience and intuition of physicians and nurses to deliver the most effective and individualized care possible with the tools that are available. But in other ways, there is everything new about the capacities we hope to develop in the coming years: molecular-based diagnostics and therapy development, supported in the clinic and at home by modern information technology.

We have the prospect of new medical tools that will:

- help us achieve the right diagnosis and prescribe the right medication for the particular individual and exact condition, steadily improving on traditional trial-and-error approaches;
- enable us to spot the onset of disease even before symptoms appear, and take action to preempt or delay onset of the condition; and
- help us identify our own predisposition to disease, so that we can take more effective steps to prevent it.

And with a widespread foundation of interoperable health information technology, consumers and providers should have:

- fast and reliable access to their personal health data in an electronic health record, perhaps even including their own genetic profile;
- new software support tools to help them make the best decisions based on their own personal health data and the particular characteristics of a disease; and
- the opportunity to take part in a “learning health care system,” where data from very large numbers of patients and clinical encounters will support much more rapid learning and new opportunities for individualizing care.

This marriage of new biological knowledge with new information tools is a powerful combination. Yet there is another element to this vision of the possible future. Personalized health care is not only about precision and effectiveness for practitioners – it is also about a new role for the consumer and patient. It’s about a future in which medical information will be not only better, but also more accessible. As the number of factors involved in health care decision-making become more than a human brain can process, we will develop informatics tools to make those factors manageable. Over time, these tools will surely not remain confined to health care professionals – they’ll become available to consumers as well. So a wealth of understandable and actionable health information will emerge – and that will have the effect of democratizing the process of health care itself.

The “person” in personalized health care is at the core of the change that I anticipate. Clinicians will indeed be enabled to diagnose and treat with ever-greater precision. But at the same time, a growing role for the patient as decision-maker, supported by new information tools, will be a prominent feature marking a new age of personalized health care. To my mind, this can only enhance the ability of the practitioner to help patients achieve the best possible life-long health.

What will personalized health care look like? And how might each of us, as a patient, judge how “personalized” our care really is?

I would suggest six tests:

First – Do I have an electronic health record (EHR)? And in particular, do I have an EHR that is interoperable, so that it can be transmitted across different data systems securely? From a practical standpoint, the EHR is the beginning of a new level of personalization in health care. A patient’s health information, current and complete, should be available when and where it is needed in order to support the right care decisions. For the longer term, the EHR is also the foundation of other data capacities that personalize care.

Second – Does my physician provide me with a strategic plan for health maintenance, based on my own biology, family history, and other individual factors – a “Personalized Health Plan?” And do I take the responsibility to understand and act on it? Such a plan is not the same as general good-health advice. Rather it must be a personalized plan based on the patient’s own individual health factors, including risk assessment based on family health history. Over time, the strategic health plan can become increasingly sophisticated as the tools of molecular medicine are developed. But this step could – and should – be in place today.

Third – Do my physicians and other health professionals have access to decision support tools, and do they use them? And do I have access to decision support tools, as well? Decision

support applications can range from simple health and treatment reminders, to advice about prescribing and warnings about drug interactions, all the way to a future in which software tools may help us understand our own genetic profiles. The important distinction is that the guidance should increasingly be based on the patient's personal health information. An important milestone for personalized health care will be achieved when decision support tools are used as part of a patient's EHR, interacting with the data on the EHR and yielding patient-specific decision support.

Fourth – Do I have the expectation that, whenever possible, treatments will be recommended to me based on my own biology and preferences, not merely on the basis of best guesses and population averages? Patients today have high expectations of health care, but they may be unaware of how much their individual biology (as well as their own investment in the process) may affect the success or failure of a treatment. The culture of personalized health care is one in which the patient's investment in success is supported by an increasing amount and quality of individualized information. This capability will grow incrementally, but it will occur more rapidly if health care professionals and consumers alike seek out the opportunity to personalize treatment.

Fifth – Is my personal genomic or other molecular-level information available for clinical use? Ideally, is it included in my EHR, with appropriate privacy protections? This capability is the futuristic view of personalized health care – the day when key portions of our genetic profile or other molecular data, perhaps even our whole genome, may help guide health maintenance and treatment. Some genetic or other molecular testing is already available and used to steer treatments. But it is difficult to estimate how soon tests of these kinds may become the norm, or even which information may prove most useful for personal or clinical use. Nevertheless, the incorporation of personal molecular information into the EHR, with decision support tools to help understand and use that information, will mark the achievement of the classic picture of personalized health care.

Sixth – Do I have the opportunity, if I wish to do so, to contribute to new health knowledge by making my clinical information available for research, as part of a learning health care system? This is the step that completes the cycle of personalized health care. As consumers, we stand to benefit from new scientific knowledge, particularly from discoveries that apply to our own personal biologies and health needs. As patients, we can contribute to that discovery process and even help accelerate it. Discovery will come more rapidly if large amounts of clinical information are made available to researchers. The largest source of such information is ourselves – the millions of clinical encounters that take place every day. The aggregation of clinical data on a large scale should be feasible with interoperable electronic health records, although many issues including privacy protection need to be addressed in order to achieve “learning health care” systems of this kind. I regard it as the final test of personalization in health care – the ability to discover individualized treatments rapidly, and the opportunity for all patients, at their discretion, to support and accelerate medical discovery.

These six tests are meant to help show how personalized health care might work, as well as helping us measure how “personalized” our care may be. They recognize that personalized health care is a continuum: it draws on the historic aim of medicine to personalize treatment, and it builds incrementally on existing procedures to achieve a new class of personalized health tools.

These six tests do not presuppose any particular molecular-based approach. After all, it remains to be seen which approaches may prove most effective. But these tests describe the structure and health care culture that would accommodate the kinds of new tools we anticipate.

How close are we to achieving this new kind of personalized health care? In some ways and in some places, we can see movement already underway:

- A few molecular diagnostic tests already draw on genetic information to steer treatments. In cancer, HIV/AIDS and other areas, these initial products are being used to direct treatments to patients for whom the treatments will be effective. For example, testing for the HER2/neu receptor (indicating a particular form of breast cancer) can indicate the use of Herceptin for a patient, greatly increasing the effectiveness of treatment.
- Testing is underway to evaluate the efficacy of pharmacogenomics, which is the use of personal gene-based information to determine the proper drug and dosage for an individual. This effort recognizes how much more effective medical care could be, and how much more value we could achieve, if the drugs prescribed for us were the ones known to work for us, or for the subtype of disease being treated. An often-cited example is warfarin. This anticoagulant is one of our most-prescribed pharmaceuticals, but it can be accompanied by significant risks. At the present, adverse events related to warfarin are a leading cause of drug-related hospitalizations and deaths. If genetic tests can improve initial dosing of warfarin, the savings in health and dollars will be substantial: one estimate is over \$1 billion per year.
- The Food and Drug Administration already collects genetic information on a voluntary basis regarding pharmaceuticals it approves for marketing. Since the inception of the Voluntary Genomic Submission program in 2004, genetic information has been shared with FDA on some 50 drugs. This resource should help build the knowledge base for pharmacogenomic-based prescribing.
- And in a number of leading institutions, including those represented in this report, a structure of personalized health care is already being put in place. These sample case studies reflect a broad scope of approaches that are being tried, as well as new kinds of partnerships for achieving higher levels of effectiveness and personalization in health care.

In other ways, this new culture of personalized health is not at all as close as we would wish. For example, outside of major health care institutions, the adoption of health information technology and interoperable electronic health records has been painfully slow. Likewise, while the pace of discovery in science may be rapid, the development, validation and adoption of new molecular-based products and new informatics in day-to-day clinical practice will take many years or even decades.

In 2006, I launched a Personalized Health Care Initiative at HHS. The object was to help identify opportunities and coordinate activities in HHS agencies that could help accelerate a personalized health care future. Many strong efforts were already underway throughout the agencies of the Department. I saw the Initiative as an opportunity to help define the goals and build a foundation for the future that linked federal and private sector efforts.

The work of the Initiative was especially directed at preparing electronic health records to accommodate genetic test information and other elements important for personalized health care. Standards for exchanging genetic test results and embedding them in EHRs were published in 2008 and should be finalized in 2009, clearing the way for these elements to become a standard feature of EHR products in the future. Standards were also developed for EHR products to support the capture and exchange of family health history information, including development for the first time of a minimum core data set for these histories. This work will become the basis of a new, interoperable version of the Surgeon General's "My Family Health Portrait" web tool.

Other IT-related efforts carried out under the Initiative have included: recommendations concerning the confidentiality, privacy and security of genetic information in an EHR environment; development of harmonized and interoperable newborn screening information for embedding into EHRs and for public health research; recommendations for standards in pharmacogenomics, both to assist in research on drug safety and effectiveness, and for use in decision support tools in EHRs; and in collaboration with the Agency for Healthcare Research and Quality, development of clinical decision support tools to be used with EHRs.

The Initiative also inventoried some 50 programmatic activities within HHS agencies and documented them in a 2007 report, *Personalized Health Care: Opportunities, Pathways, Resources*. In addition, the Initiative commissioned a white paper regarding coverage and reimbursement issues for molecular diagnostics. It also sponsored a workshop examining new direct-to-consumer genetic information services, which began to be marketed via the Internet in late 2007.

The Initiative has been a first effort at leveraging and coordinating Department-wide activities in personalized health care. Outside the Initiative, many significant events took place: in particular, the cascade of discovery supported by the National Institutes of Health identifying newly-found associations between genetics and complex diseases; and enactment of the Genetic Information Non-discrimination Act (GINA) in May 2008. The progress in these two areas constituted significant twin milestones for genomic medicine and personalized health care. They mark both the speed with which science is providing new information and the resolution of Congress and the Administration to ensure that personal genetic information will not be misused as it enters into medical practice.

Also during this period, a pilot program supported by the Centers for Disease Control and Prevention, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), issued its first recommendations regarding the clinical usefulness of existing diagnostics. This pilot program is demonstrating a process for systematic review of clinical utility for genetic tests.

The efforts of these two years are an opening chapter – a "prologue" to a future of personalized health care. Hopefully, we have chosen productive areas in which to begin building foundations for that future. Looking forward, the period of foundation building is by no means complete. An important benchmark in the coming years will be the ability to integrate the ongoing rush of scientific discovery while simultaneously building capacities to support adoption of discoveries into everyday medical practice. Even as we balance those activities, we must continue to address the ethical, legal, social and educational issues, especially pertaining to personal genetic

information. These will be an important part of the core of trust that practitioners and consumers alike will need to feel as genetic information becomes available and useful.

Perhaps most important: the advent of personalized health care cannot take place, and should hardly even be thought about, outside the context of the present crisis in health care financing and delivery. “Crisis” is by no means too strong a word for the current condition of our health care delivery sector. Within my lifetime, overall health care costs have grown from 4 percent of gross domestic product in 1951 to 16 percent today, and headed to 20 percent by 2016. This trend is not sustainable.

Of course, it is true that medical care today is much more powerful than it was in the 1950s. It is also true that the United States has led the way in forging medical progress. But at the same time, our health care spending per person is on the order of twice that of other nations whose health status is equal to or better than ours. And despite this level of spending, which is more than the total gross domestic products of all but a few nations, some 45 million Americans are without health coverage. How has this happened?

An important element of the problem lies with the outdated system of reimbursement that is enshrined in the Medicare program. Medicare is far and away our largest health care payor, and its systems are used as a model for most of the rest of our health care delivery sector.

Unfortunately, the payment approach that Medicare has enshrined is based on piecemeal payment for services, where reimbursement is only tangentially related to quality, and almost entirely unrelated to the patient outcomes. As such, Medicare is a government-run, price fixing system where payment is based on volume rather than value. It has few mechanisms for supporting preventive health care or sharing the value realized when an expensive procedure or health condition is avoided. And to make the storm perfect, Medicare is an open-ended entitlement program without the discipline of a global budget.

With the Medicare model serving as our central paradigm for health care payment, we have a system that engenders “silo syndrome” – that is, there is little coordination among caregivers; a system whose main incentive is the “chronic more” – that is, the incentives reward more care, rather than better care; and a system where payments are indifferent to quality – that is, we pay the same for poor quality as we do for excellent quality. We rely on our practitioners to deliver the best care they can, but we reward them financially only for volume. There is virtually no financial reward provided to them for getting a diagnosis and treatment right on the first encounter, or for spotting disease early and avoiding costly procedures, or for helping patients understand their personal long-term health risks or supporting actions that may preserve good health.

Proposals for health care reform are often focused on problems of cost or access to insurance and care. But in fact, to be successful, reform needs to focus on the intertwined complex of three factors: affordability, accessibility and value. We will not achieve affordability and improved access without building value into our health care system. By that I mean medically effective care at a cost-effective price.



To achieve these goals in a sector as large and tangled as health care, we need to start by asking: What can empower all those who are caught in this web to move in a common direction toward the results we want? During my term as HHS Secretary, I have focused on constructing a consensus-based foundation anchored on four “cornerstones:”

The first cornerstone must be quality standards. If the object is to achieve high value for our health care dollars, then we must be able to measure the quality of the care – either in terms of recognized standards of practice, or in terms of outcome for the patient, or both. This is not about “cookie-cutter” medicine. It is about a consensus process for learning and applying what works, based on scientific evidence. Quality measurement will support quality comparison – and carried out properly, it will lead to continual improvement in care.

The second cornerstone is cost comparison. With standards for quality in place, we will be enabled for the first time to make cost comparisons in health care as we do in other markets. We will not be confined to looking only at the dollar amounts, but at the quality and value we are purchasing in combination with the price. Intelligent cost comparison will call on us to use devices like single prices for medical procedures, instead of piecemeal charging for each part of the procedure. It will also challenge us to assess and pay for the true long-term value of preventive care.

The third cornerstone is interoperable health information technology. Our health information base needs to be vastly better than at present. This includes information at the most fundamental level – the patient health record – as well as our processes for gathering and understanding data, and our ability to share information among providers and others in order to improve care.

The fourth cornerstone is incentives to reward the results we want – namely, good care and good health. Our payment systems need to identify and reward the delivery of high quality care in a cost-effective manner: value.

These four cornerstones are key enablers of change and improvement in health care. They drive positive change because they enable stakeholders throughout the health care sector to seek their own advantage by seeking value. As such, I believe they are the underlying keys to health care reform. I also believe personalized health care is an important element at the heart of these enabling factors:

- The development of quality standards is inherent in personalized care. “Personalizing” care means knowing what works, knowing why it works, knowing who it works for, and applying that knowledge for patients. Approaching health care in this manner is virtually synonymous with the application of quality standards. As a further bonus, the drive to differentiate care at increasingly well-defined sub-populations could help ensure that standards of care will not stagnate.
- Personalized health care also points toward a promising new dimension of cost comparison and cost saving. By using new diagnostic tools to help identify the most effective treatment options for a patient, personalized health care promises to help avoid ineffective treatments and the associated costs. In addition, new knowledge about associations between molecular factors and health conditions should help identify disease

early and point toward effective prevention. It should be possible to identify the point at which a given product or service becomes cost-effective by avoiding ineffective treatments or costly future procedures, or by preventing disease.

- The development of new data capabilities, based on interoperable health information technology, is also integral to personalized health care. Increasing differentiation of care will require a new scope in our knowledge base and new kinds of data networking. It will require the ability to aggregate very large volumes of data, through interoperable health information technology – as well as new informatics tools to achieve rapid analysis of the data and propel further research.

Thus, personalized health care should be an explicit goal of health care reform. And the developers of products and services that personalize health care need to understand that their success depends on delivering results that serve the conjoined goals of affordability, accessibility and value.

As Secretary of Health and Human Services, I have had the privilege of taking new steps toward better health for Americans, and indeed toward improved global health. I built on the work of those who preceded me. Now I feel the importance of passing on to my successors what I have learned – a “note on the desk” that may be helpful to them

My note about personalized health care would start this way:

Personalizing health care is not a niche concern. Its promise is central to the future of health care. It gathers the newest and most promising scientific knowledge and directs it in a coherent way at the oldest and best intentions of medicine. It asks the right questions and applies the right tests as we seek a better health care system delivering better value and better health status for our citizens.

My note would go on to point toward four areas that I think are in play at this time of hand-off:

First, the base of interoperable health information technology is critical and remains far from complete. It is not merely a matter of electronic health records, but equally the capacity to exchange information securely. This is crucial for practitioners as the elements of care become more complex, and it is crucial for research and medical progress. Consensus-based standards are at the heart of this effort.

Second, as data accumulates ever-more rapidly and the demand for standards increases, we will need to focus on the question of what constitutes actionable medical evidence. It will become increasingly important to have defined standards of evidence that will satisfy doctors and patients as they make health decisions, and that will be useful for regulatory and reimbursement purposes.

Third, personalized health care will require new business models and reimbursement approaches. Our health care system is tilted strongly toward post-symptomatic treatment and volume-driven payment. But with personalized health care, we hope to detect disease earlier and prevent it more effectively. We will need to learn to quantify that value and reward it appropriately.

Fourth, personalized health care is about developing new kinds of information and services – but it must equally be about using that information properly. Physicians and other health care professionals need to be engaged in the process of change. And consumers will need a growing information and education base.

I would conclude my note with two thoughts about the role of government in particular:

First would be the importance of building “translation” into the scientific enterprise. Government, and HHS in particular, has a primary role in supporting scientific discovery. We need to work closely with the medical community to improve the translation of proven techniques “from bench to bedside.”

Second, I would call attention to the potential for closer alignment of the work of the FDA and the Centers for Medicare & Medicaid Services. In particular this pertains to the issue of standards of evidence, especially for products and services that reduce costs in the future by identifying disease earlier or enabling effective prevention. Such tools would represent a new paradigm in medical care, and they may require new ways of assessing and rewarding for the value of costs that are avoided. The different missions and capabilities of FDA and CMS will both be needed to usher in these tools, and I believe a new kind of collaboration between them could be important for progress.

One important question remains: How long? When may the promise of personalized health care be realized?

I see it as the work of a generation. It is already a national goal to achieve secure, interoperable electronic health records for most Americans in five years. My hope is that in ten years, it will be the norm for consumers and practitioners to anticipate that treatments should be individually targeted, with diagnostics and therapies commonly associated as a paired unit. Within 15 years, I hope that major clinical data sources can be securely linked in a manner that gives most Americans the option of allowing their own de-identified health information to be employed in the quest for ever-more individualized understanding of health and disease. And within 20 years, I hope that data and informatics will have advanced to the point of supporting meaningful individual prediction regarding an individual’s life-long health prospects, including specific, proven steps that he or she can take to protect and enhance health.

Personalized health information, based on individual biology, yielding increasingly precise and predictive health care: these are the goals of personalized health care. Progress toward them will no doubt seem slower than we wish. But over time, I believe personalized health care will be even more transformative than we can imagine.

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# Commissioned Papers



# Personalized Health Management: A Geisinger View

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Geisinger Health Systems

## INTRODUCTION

The US healthcare system is beset with persistent structural challenges that continue to erode the quality of care while simultaneously increasing cost and hindering access (1-4). Structural changes in how care is delivered and financed will be required to overcome these challenges, as will a fundamental shift away from the traditional role of what it means to be a patient in the U.S. healthcare system. We believe the latter shift will involve a cultural change in how the individual is viewed, transitioning from a classic “patient role” to an engaged “*consumer role.*” In this paper, we set forth the concept of “personal health management” (PHM) to describe a *process*, supported by a set of *tools* and *technologies*, in which consumers assume an increasingly active role in how their health is managed, in personalizing the value proposition of their purchased health care services, and in determining how and which health care services they use. With deliberate meaning and intent, we use the terms “consumer” and “patient”, respectively, to distinguish “a shift towards more control” versus “a passive participant in a care process”. In this paper, we describe the vision for PHM at Geisinger, where innovative processes, supported by a set of tools and technologies, are adopted based on sensible business principles and payor-linked incentives, all with the purpose of changing behavior to move from a provider-centric to a consumer-centric model.

We currently envision seven objectives essential to implementing a fully developed PHM model. Objectives 1 and 2 provide the foundation for all other objectives. Objectives 3-4 support the

consumer. Objective 5 supports the provider. Objectives 6 and 7 facilitate consumer-provider communications.

1. All data relevant to consumer PHM should be valid, integrated, and readily accessible.
2. Health care and information access channels should be diversified to provide for timely and efficient encounters.
3. Encounters should be based on content specific, personalized, consumer relevant data.
4. Where sensible, encounters should be informed by consumer choice.
5. Clinicians should have ready access to the right data, information, and expert guidance.
6. Shared decision making should be seamless and routine during every encounter
7. PHM should be dynamic, guided by consumer preferences, current status, and evidence.

One of the hallmarks of the US healthcare system is the persistent lack of alignment among payors, providers, employers, and consumers to achieve high-quality care in a cost-effective way (5). Indeed, there is no single stakeholder who is focused on the overall value of the care process (i.e. optimizing the incentives and objectives of ALL stakeholders). Cost-shifting among stakeholders (i.e., employers, insurers, providers) has been the dominant means of solving periodic market or policy challenges (6). Consumers are the latest to “participate” in these cost shifting efforts via high deductible plans and so-called “consumer-directed” plans (7), a change that reflects the extreme pressures on US employers to reduce the impact of healthcare coverage on their bottom line, paralleling the shift from defined benefit to defined contribution retirement plans(8). These plans have been successful in realigning incentives, but without a concomitant change to the delivery system or tools needed to navigate it; furthermore, these consumer-directed initiatives do not inherently satisfy any of the primary objectives of PHM.

In many ways, the anatomy of Geisinger as an integrated delivery system – with its multiple hospitals, a geographically-dispersed multi-specialty group practice, and a separate (non-exclusive) insurer – make it a microcosm of the larger US healthcare system, struggling to meet the challenge of aligning incentives and processes to satisfy its major stakeholders. Specifically, throughout the Geisinger service area and throughout the US, the greatest *near-term* strategic/political challenges are financial - per-capita costs are increasing, patient average age is increasing, per-capita clinician supply is decreasing, and below-cost payers (e.g., Medicare, Medicaid) are becoming the increasingly predominant payor. As a business imperative, Geisinger is seeking to close the gap between what Medicare pays and what it costs to provide care. We believe that PHM is central to closing this gap.

Our belief in the potential to alter a complex marketplace through empowering the consumer is not without precedent. The financial planning market was once dominated by a paternalistic model in which high-quality advice and information were available through “knowledgeable experts” primarily to those with the resources to pay for it. With the transition from defined-benefit to defined-contribution pension plans, a consumer focused shift was inevitable. Subsequently, new *tools* and *processes* (e.g. web-based asset allocation guidance, online trading, etc) were developed that effectively allowed consumers to become, if they so desired, their own financial planners. In this environment, consumers are allowed to make “bad decisions” (e.g., sole selection of a money market account), if they want to, without a “parental influence” over what they do. At the same time, they are guided by increasingly sophisticated, but easy-to-use programs (e.g., risk profiling tools that map to fund allocations, automated rebalancing, age-based shifts in asset allocation, etc.) that rival even the most expert financial advisors in terms of

performance. The focus is on providing the consumer with high quality information, tools and back-up human support; while the business seeks to influence the selection of an “optimal” choice, it doesn’t feel “responsible” for their ultimate choice. Although not without challenges, few can argue that the revolution in financial planning has increased access, reduced costs and dramatically improved financial performance for many millions of consumers.

In the sections that follow, we describe in greater detail the key elements, process and tools that will be important to our PHM model, followed by our five year plan.

## **PHM OBJECTIVES**

In this section, we consider the primary needs of and challenges faced by both consumers and providers as their roles evolve in a PHM model. We also outline the processes and tools relevant to the PHM objectives, with a specific focus on tools and processes that integrate multiple data sources and integrate with our EHR. Throughout this paper we use the terms “tools” and “processes.” *Tools* serve a single function (e.g., data capture) whereas *processes* involve two or more tools that are linked and/or functionally dependent (e.g., patient data capture and clinical decision support) or represent an existing human process transformed by the introduction on a new tool.

Health care reform efforts over the past 30 years have essentially been focused on “tinkering” with the existing system, rather than systematically reengineering processes to support consumers and providers in a consumer centric model. Health information technology is critical to reform efforts (9, 10). Use of an electronic health record (EHR), in particular, is proving to be critical to re-engineering processes - importantly, though, not as a self-contained solution, but rather as a multi-process/tool integration platform. We view the EHR as an important focal point for the development of new processes and for the development of supporting tools that will diversify options for providing, managing, and monitoring care. Additionally, we believe that the development of tools that interact with, but which are distinct from, the EHR represent a market segment with the potential to spawn rapid, industry-changing innovations as individuals, companies, and health care systems seek to capitalize on the opportunity.

### **Objectives 1 and 2: Foundational**

Real-time unfettered access to data from disparate sources, including an EHR, is essential for the continuous evolution towards a PHM model. We consider our own work in this regard and implications for PHM, recognizing that there is more than one solution. In the past 24 months, to satisfy several explicit business needs, Geisinger has created a comprehensive enterprise-level data warehouse, a resource that has transformed our thinking of what is possible. The warehouse receives feeds from multiple source systems, including our EHR, financial decision support, claims, patient satisfaction and high-use 3<sup>rd</sup>-party reference datasets. The source data are transformed through a standard “Extract-Transform-Load” (ETL) process. Expansion to additional data source systems (e.g., niche specialty systems such as oncology) is being accomplished in stages and will eventually encompass all high-value data sources. While the warehouse will significantly advance our ability to perform traditional activities such as performance reporting, trending, self-service data access and other similar tasks, the most important value of the data warehouse is as a foundation for advanced analytics and as an automated real-time data source for PHM processes, enabling what we describe as our Clinical Decision Intelligence System (“CDIS”). Because CDIS represents a standardized, normalized,



multi-year dataset for our entire population that is accessible using intuitive yet robust business intelligence applications, it serves as an ideal analytic foundation. Current examples include mining the database to identify patients in need of certain interventions prior to a visit (e.g., diabetics with a HgbA1c > 7 for at least two of the past four quarters), identifying “open loops” (e.g., all patients with a positive PSA test without a visit to a urologist, an intervention or a subsequently normal PSA within 3 months) and identifying correlations in treatment and outcomes (e.g., association of patients in payor class x who fail to fill a prescription for disease y). We anticipate that CDIS will serve as the primary historical data feed for our PHM tools, for performance trending and as a near real-time source for data back into our EHR. It is also likely to be a resource to retain and effectively use many different types of derivative and reference data (e.g., libraries of clinical rules, data capture tools, community resources and other geographic information based data sources, insurance costs, co-pays, formularies, etc).

In any clinical business, physical space is expensive and costs (e.g., maintenance, utilities) are likely to increase over time. For this reason, many businesses adopt metrics that are designed to encourage optimal use of space (e.g. revenue per square foot). In healthcare settings, clinic space itself is frequently used in an inefficient manner. For example, large waiting areas serve as a holding space to ensure that exam rooms are efficiently used, but the waiting area itself is not simultaneously used as a “working” area. It largely represents an inefficient use of space. Converting waiting areas to exam or working areas, where privacy is assured increases the amount of active clinical space and provides the means to put consumers to “work” shortly after they arrive in a clinic (e.g., educational or data gathering kiosks in the exam room, group therapy rooms). More generally, largely confining care encounters to the traditional clinic space limits consumer access both because it takes time to get to a clinic and transportation costs are increasingly material to the consumer. PHM should be devised to ensure ready access to care, where the mode of access is tailored to the level of consumer need, risks, complexity, etc (Table 1). Leveraging a diversity of access channels (e.g., retail clinics, guided email exchange, remote online encounters, phone calls, remote monitoring, telemedicine, etc.) can both dramatically increase timely access and reduce the total cost of an encounter.

### **Objectives 3 and 4: Supporting the Consumer**

Individuals utilize health services for varied reasons: because they want to maintain optimal health, because they are aware of or concerned they may have a health problem, or because they seek resolution for specific acute and/or urgent problems. When consumers have a defined health problem, and even as they seek to maintain health, they generally want assurance that their chosen course of action is reasonable/feasible or, in some cases, that “doing nothing” is a sensible approach to care. Meeting these needs requires bi-directional communication between consumers and their various decision support resources; specifically, consumers want to know what health and/or lifestyle behaviors can benefit them, what the associated cost will be, and what, if any, evidence exists to support the comparative value of available interventions (e.g., probability of a positive outcomes, risks, uncertainties, etc). If action is taken, the consumer needs to know (in real-time, to the degree possible) how well the intervention is working; if it isn’t working, consumers need to know whether a change in strategy is required. At the same time, consumers will seek to provide information and feedback to their clinician (e.g., risk tolerance, preferences for specific interventions or therapeutic modalities, symptom reporting, affordability factors, etc) so that the development and modification of the care plan reconciles what the consumer *should* do, optimizing the intersection with what they *want* and are *likely* to

do. Our goal for PHM is to meet these needs by systematically eliciting information from consumers and by facilitating their ability to assume substantial decision responsibility and control. Some consumers will make seemingly irrational choices (e.g., “I do not want to do anything about my diabetic risk of limb loss”). Importantly, this kind of choice is crucial to communicate to the provider as a key point for discussion, and one that would remain “hidden” and result in deleterious “non compliance” if not explicitly identified and addressed. A growing literature indicates that value added processes already enable patients to successfully contribute subjective and objective information, preferences, and responses to therapies and to manage treatments themselves (11, 12).

### **Obtaining Data and Information**

The method by which patient-specific information is obtained on a patient has not changed substantially over the past century, even though office visit time and reimbursements have become increasingly constrained. Most verbal interactions between providers and patients occur in a somewhat unstructured manner. Information gathering, documentation, and interpretation are unsystematic and unnecessarily consume precious time from providers. Fortunately, much of the data currently obtained through conversation can be collected from the consumer before the clinician encounter via automated interactions (e.g. exam room-based touch screen enabled screening tools). By so doing, the breadth, depth, quality and utility of those data can be substantially improved, the efficiency of care processes can be increased, clinicians will be better informed, and the reimbursement value of a visit can be increased. Importantly, use of such a process provides the means to re-purpose data (e.g., provider guidance, tailoring intervention options to patient features and preferences, patient education, informed decision making, etc) in ways that give the patient an active voice in the care process and a means to guide their own decision-making.

Over the last 30 years, researchers have developed myriad valid patient-completed questionnaires intended to facilitate administrative management and clinical care decision-making. While potentially useful, existing questionnaires have not been widely used in traditional paper-based practice settings because the workflow is problematic (e.g., provider must interact with the patient while reading the questionnaire), the administrative task associated with choosing questionnaires and interpreting responses (e.g., scoring) is burdensome, the impact on the sequence and timing of existing work flows is difficult and their use in care planning/surveillance is not standardized.

We view use of patient reported data capture tools as a cornerstone to virtually every other process we envision to support consumers and providers. Beginning in 2003, we experimented with different approaches (i.e., digital pen, scan form, pen tab, touch screen) and workflows (i.e., web portal, waiting area, exam room, etc.) to integrate patient data capture and use of such data in real time as a routine part of the care process. This work continues with a comprehensive strategy to capture and interactively use patient-reported data on diagnostics, medication reconciliation, review of systems, preferences solicitation, outcomes monitoring, etc, to: 1) optimize the settings, timing and reliability of patient-reported data capture for clinical purposes; 2) optimize the accuracy, completeness, specificity and utility of patient-reported data for clinical and administrative purposes; 3) minimize the workload burden - for patients and staff - associated with obtaining data; and 4) fully inform the provider. Our long term strategy will rely on the use of a Patient Reported Data Acquisition and Management System (PARDAMS), that

integrates the following: 1) a rules engine that decides which questionnaire module should be used to collect data from a patient before (e.g., screening), during (e.g. diagnostics), or after (e.g., outcomes) a given encounter; 2) a library of well validated questionnaires, with an increasing emphasis on sophisticated use of branching logic and on the use of dynamic questionnaires for assessing outcomes; and 3) a rules engine that intersects the information gained via the questionnaire along with data in our other systems and tools (e.g. data warehouse, decision support engine) to recommend some form of action.

### Consumer Choice

When a consumer seeks care, they usually face a complex process over which they have relatively little perceived control. The patient is often a passive recipient of information, where comprehension may vary substantially and is rarely verified. We believe that consumer control, consumer activation, and improved efficiency and quality of care can be achieved through the use of sophisticated automated and semi-automated consumer guides. We do not think it is relevant to ask “do patients *want* to assume control?” Rather, the more sensible question is “how can systems, processes, and tools be designed to motivate the consumer to be in control?” To some degree, the lack of consumer control is a failure of the delivery system. In this section, we first consider factors that will influence the level of consumer control that is sensible and then specifically consider tools that will be useful in this process.

The following factors are likely to be important in directly or indirectly influencing the appropriate level of control chosen by the consumer: 1) level of risk (mortality, side effects, etc.);

Table 1. Relation between how much decision control and intervention control the consumer can assume in relation to the risk from intervention, quality of evidence, complexity of the decision process or intervention

RISK	EVIDENCE	DECISION COMPLEXITY			INTERVENTION COMPLEXITY		
		LOW	MOD.	HIGH	LOW	MOD.	HIGH
LOW	LOW						
	MOD.						
	HIGH						
MODERATE (MOD)	LOW						
	MOD.						
	HIGH						
HIGH	LOW						
	MOD.						
	HIGH						
Color key for relative degree of involvement of patient, physician and other providers		Strong patient role			Equal role		Strong physician role
		Moderate patient role			Moderate physician role		Physician & Other Support <sup>1</sup>

<sup>1</sup>Includes mid-level providers, dietitians, social workers for decision support and nurses and other support staff to facilitate logistics and administrative processing

2) strength of the research-based evidence, 3) complexity of the decision, and 4) complexity of the recommended intervention (Table 1). To some degree, these same factors will dictate features of the system required to support control. Where evidence about what to do is robust and understandable (e.g., management of hypertension, hyperlipidemia, etc), risks are low, and within the limits of common sense, we believe that as much control as possible should be shifted to the consumer (Table 1). Where the risk of confusion and of making the “wrong decision” increase (e.g., as decision complexity increases), consumer-oriented decision support tools may become increasingly important and useful. In those cases, consumer guidance can be used to simultaneously educate and facilitate thoughtful discussion and decision making.

We envision and are already testing a number of tools relevant to this process. Together, these tools should eventually provide the means for comprehensive guidance (e.g., age appropriate guide regarding near-term needs and longer-term needs for middle age, older age, and near death phases of life) and health management planning/evaluation. We specifically consider pre/post-encounter summaries and interactive preference-based guides (e.g., computerized tools that guide consumers through choices while educating them about risks, benefits, costs, etc). Encounters should be accompanied by a pre-encounter summary that verifies the encounter's purpose and expectations as well as a post-encounter summary that includes the visit purpose, key information provided by the consumer, the agreed-upon care plan, the established follow-up goals, the clinician orders (e.g., any follow-up visits) and educational information (including references to any other sources of information). Pre/post-visit guides should be routinely voiced at an appropriate education level and in a patient-preferred form (e.g., print, email, fax, etc). Whenever possible, consumers should be able to use interactive tools that serve to both achieve pre-visit work and to guide a preference-based decision process. For example, guidance could be offered on risks, benefits, uncertainties, and costs of any decision consumers need to make. Accurate representation of facts in a preferred presentation form will be essential, as will more nuanced information about the relative certainty of those "facts". Moreover, where an intervention is deemed necessary, comparative provider performance metrics should be readily accessible and visually intuitive. Such a decision support process can be designed to systematically guide consumers, respond to specific information they provide, obtain feedback on comprehension, and effectively communicate with a provider the consumer's decisions and uncertainties.

The intention behind evolving consumer guidance clearly is not to eliminate clinicians, but rather to allow clinicians to be more focused on the important tasks that are less likely to be done in today's environment (e.g., planning and overseeing comprehensive care plans, discussing difficult trade-off decisions) and to optimize the full use of the skills and training of each member of the care team (e.g., nurses, pharmacists, PAs, NPs, and other mid-levels). In the future, providers may offer the greatest value to consumers where the risks (e.g., of preventable mortality, excess utilization, adverse event, excess cost, etc.) for deciding what to do are moderate to high and where the evidence to support these decisions is low to moderate or where the provider has access to comprehensive information on what the consumer wants. We recognize that there are areas where the evidence about treatment options is unclear or inconsistent, as well as, instances for which the evidence will fail to account for clinical and/or patient-specific nuances. Moreover, certain consumers are less likely to be comfortable in this model. Finally, we do not assume that every consumer will achieve full adoption of the PHM model or that the consumer is ultimately responsible for *all* decision-making; rather, that well-designed PHM tools can play an important role in determining when physician or other provider involvement is crucial, when it is optional and when self-care is sufficient. We expect the relative involvement of consumers and various providers will vary substantially by different types of health problems (Table 1) as will the value proposition to payors and employers.

#### **Objective 5: Supporting the Clinician**

PHM will not be possible unless there is a compelling value proposition that fosters clinician adoption. In our view, this means that the PHM process must offer a competitive edge to clinicians by improving their efficiency, consumer satisfaction, clinical outcomes and/or profitability. We fully realize that this is a lofty goal. We consider examples of processes and

tools currently under development or being considered at Geisinger that are relevant to objective 5.

***Problem List Management:*** Physicians regularly collect, review, analyze, and synthesize patient data to diagnose, treat, and provide longitudinal care for patients. The concept of the problem-oriented medical record (POMR) grew from a need to effectively arrange and display patient medical information to enable other medical practitioners to appreciate the thoroughness of the data-gathering process and to follow the logic of the resulting diagnostic conclusions and treatment recommendations. The problem list is important to PHM because it is intimately linked to patient data capture, continuous care protocols, automated decision support, etc. In an electronic environment, the problem list offers new opportunities (e.g., when diagnoses are captured electronically, automated, tailored decision support is possible). However, coding practices and naming conventions vary widely, to the point that data in the EHR is often unreliable. The Problem List is also a shared resource in an EHR environment, introducing a new set of challenges and barriers to reliability, credibility, and utility. Based on experience within our own system, we believe that tools that encompass automated protocols for perpetual management of Problem List entries will be critical to address: a) *Outdated Information* (e.g., diagnoses that are old and/or no longer apply); b) *Wrong Information* (e.g., diagnoses that are inaccurate); c) *Suboptimal Coding* (e.g., diagnoses that are correct but lack appropriate specificity); d) *Redundancy* (i.e., multiple diagnoses that describe the same condition/problem); e) *Inconsistent Terminology* (i.e., naming conventions that, although perhaps standardized like the ICD schema, do not correspond well with terminology used by clinicians or consumers); f) *Disorder* (i.e., non-prioritized sequencing and/or illogical grouping that inhibits the user from easily/reliably visualizing and considering the full complement of actionable diagnoses); and g) *Missing Information* (e.g., diagnoses associated with post-encounter and/or 3<sup>rd</sup>-party test results).

### **Risk Assessment and Stratification**

Quantitative risk calculations provide the means for more focused and actionable feedback to consumers and clinicians and offer a means to stratify patients by risk and related care management options. We are currently testing the use of risk calculators for diabetes related macro/micro-vascular risks and for cardiovascular risk in general as a means to communicate to consumers and clinicians. These and other such tools make use of EHR and patient reported data. We will use risk assessment tools for shared decision making processes, to provide clinicians with expert clinical guidance, and sometimes as a global outcome where a number of quantifiable factors mediate the endpoint of interest (e.g., macro/micro-vascular risk in patients with diabetes).

### **Personalized Prediction Models**

Population-level longitudinal EHR data is useful in developing prediction models that are sensitive and specific to patient subgroups that differ by history, treatment status and genetic profile. The development, validation, and real time use of such models is highly relevant to PHM. For example, we recently used EHR data to develop and validate a model for predicting diagnosis of heart failure among primary care patients. A robust model was developed that detects heart failure, on average, 15 months before it is usually diagnosed. We believe that incorporation of this risk model in to the usual care process will facilitate early detection of heart failure and provide the means to influence the natural history of the disease in patients who would otherwise be detected at a later time.

### **Visual Display of Clinical Information**

As the management requirement of increasingly complex costly treatment regimens (e.g., biologic medications) for patients with multiple chronic diseases has multiplied, it has become increasingly difficult for clinicians to find, aggregate and confidently visualize all of the clinical information that is pertinent to a given encounter. In recent work at Geisinger, rheumatologists estimated that even with a fully-functional EHR, it would take an average of 15 minutes to fully review patient data to ensure that a treatment decision was optimal; on average, physicians have 2 to 3 minutes. The EHR makes data can be readily more readily accessible, but not necessarily in an efficient, intuitive and integrated manner. To address this gap, we are developing a web-based dashboard designed to display temporal profiles of patient reported functional status and other questionnaire-based measures, lab data relevant to toxicity, EHR data on current treatments, and other clinically relevant items. The dashboard, which will be accessed via a hyperlink within the EHR, also includes structured text fields to be completed by the nurse and physician. Draft progress notes and a patient after-visit summary will be automatically assembled through the interaction with the dashboard and imported into the EHR after the physician closes the hyperlink. Currently, the display features of the dashboard are not possible to create within the EHR. We believe this work is relevant to other medical specialties, as it provides a means to instantaneously display diverse data to facilitate efficient clinical decision making, without the imposition of EHR vendor-specific constraints on the use of and display of data.

### **Clinical Decision Support (CDS)**

The development and promulgation of clinical guidelines, an activity which emerged in the early 1990s, has been a prolific enterprise focused on codifying disease-specific clinical knowledge intended to, in part, promote the delivery of evidence-based care. Adoption of guidelines in practice, however, has not been successful(1), especially in primary care and for the elderly (13). This is not surprising, as it is impractical to assume that clinicians can gather, winnow, and synthesize the ever-expanding and often-conflicting body of available evidence and research or that they can ever be up-to-date through CME or other modes of education.

Translating knowledge to practice (i.e., reliable efficient role-optimized operational work flows) must address a number of important realities. First, for primary care physicians, the rate of newly-generated relevant clinical guidelines far exceeds the time available to understand and assimilate them.. CME alone is not a solution. Second, guidelines are often stakeholder centric: disease-specific guidelines are generally developed by specialists, whereas primary care providers may treat the majority of cases. Translation to primary care is also hampered by the “siloesd” nature of guidelines; whereas guidelines are developed for a specific condition, there are few or no guidelines that address appropriate treatments for patients with more than one condition. Furthermore, if all applicable guidelines were applied to a patient, the resulting treatment regimen would likely include multiple medications with high complexity, a risk for drug interactions, the potential for adverse drug events, and an unsustainable treatment burden (13). Third, knowledge of what to do is only one part of what is required to make the best decision on behalf of a patient. Other necessary steps – including accessing relevant patient data (a potentially time consuming process) and retrieving and interpreting the right knowledge in light of data – mediate the ultimate decision. Based on recent experience, we believe that two types of tools will be essential to bring actionable and timely knowledge to the point of care:

1) tools that identify, extract, and evaluate patient data in real time; and 2) tools that translate output from rules processes into readily interpretable actionable advice. While it would be ideal if EHRs or PHRs fulfilled these functions, our experience over the past three years indicates that this is not likely to be the case anytime soon, if at all. Ideally, clinician CDS should facilitate making optimized decisions that are based on detailed knowledge about the patient, their preferences and the best available applicable evidence

### **Objective 6: Shared Decision Making**

Without a business sensible process, we do not expect providers to systematically engage in shared decision making (SDM) care processes with patients on a routine basis. Practically, SDM is too time consuming and, without incremental reimbursement, not cost effective. We do not envision that research on ways to foster such behavior on the part of patients or providers will be fruitful unless tools are developed to make such interactions cost effective. On the other hand, we believe that patient-completed data capture tools and interactive consumer guides provide the foundation for related tools that efficiently inform the provider of the patient's choices and naturally foster SDM as part of the process. Patient completed questionnaires combined with risk calculators and SDM tools can be used to increase the level of productivity during an encounter without increasing the workload. We are investing in the development and use of such tools for management of CVD risk and risk of vascular events in diabetics. Our objectives in the use of these tools are: 1) educate patients about risk factors; 2) engage patients in choosing interventions to manage risk factors, including an option to do nothing; 3) understand the intervention(s) that offer the greatest benefit; and 4) seamlessly inform the provider during the encounter of the patient's choices, or lack thereof, so that the care plan incorporates this information.

### **Objective 7: Continuous Management**

Continuous management is logistically complex and, accordingly, subject to failure. Effective continuous management requires systematic periodic consumer-clinician interactions, data evaluation, and PHM plan changes. In practice, the first 6 PHM objectives lead to the establishment of an agreed-upon goal or set of goals for managing health problems and related risk factors. By definition, goals – which can be reflected as either subjective (e.g. quality of life) or objective (e.g. LDL) measures – need to be modifiable and actionable. The continuous management process involves a schedule of consumer-clinician interactions designed to review current status (e.g., progress relative to agreed upon goals) which, in turn, requires perpetual updating of the treatment plan. A discussion of current status can involve a consideration of satisfaction with treatment, the need to modify goals and/or modifications to the treatment plan itself. The continuous management process also involves safety monitoring and re-evaluation of risk.

Our "e-Rheumatology" project illustrates this how a continuous care process might work in the future. In one panel of a dashboard, trend lines of pain and functioning scores (based on patient self reported data) are displayed along with other relevant data (e.g., treatments prescribed, toxicity measures). In the same panel, goals for specific measures can be documented, based on patient and physician discussion. Documentation of the agreed upon goal is also automatically copied to other panels (e.g., after visit summary, draft progress notes) along with other relevant data, to ensure continuity and accuracy of communication. Lastly, the next visit is scheduled in relation to the urgency for care and/or changes in patient goals/treatment plan.

## **PHM IMPLEMENTATION AT GEISINGER**

In this section, we describe more fully our plan for implementing PHM at Geisinger over the next five years. We are increasingly adopting a view that PHM will require that many new processes be developed external to the EHR. Hard coding processes and tools within the EHR is largely incremental and framed by a process improvement model. The disadvantage of this approach is that solutions are highly constrained. Moreover, maintaining software libraries of idiosyncratic functions becomes increasingly demanding and burdensome, especially when version changes in the EHR software occur. In this section, we focus on an alternative approach that is based on the development of tools and processes independent of the EHR. These tools and processes can be designed to interact with the EHR, an interoperable data warehouse, or other tools and processes, but the approach to development is not constrained by the need to modify the EHR itself.

The processes and tools that we have discussed in this paper vary substantially in their stage of development. A number of the tools (e.g., touch screen questionnaires, visual displays of data, interactive tools for patients, CDS) are currently being developed and tested in early pilot work, while others are still at the conceptual stage. We expect that, as we evolve PHM over time, we will identify other important elements, processes, and tools. For example, we recently concluded that a uniquely defined test environment – developed in conjunction with, but distinct from, the corporate IT environment – is essential to accelerate and diversify the discovery and development of novel IT solutions. The need for system level policies and procedures to ensure information security and compliance with regulations, while important to the process of care delivery, is a barrier to research on and innovation in the use of IT in health care. These restrictions can dramatically limit efforts to experiment with novel IT solutions. In response, Geisinger has recently developed administrative and IT solutions to ensure system level security, while providing the flexibility needed for unrestricted ability to build and test prototype applications.

Geisinger's implementation of PHM has and will continue to involve deliberate change to existing care models, motivated by an interest to create increasingly efficient, higher quality, and more effective care. Where relevant, migrating towards information-rich virtual and semi-virtual encounters is an important part of our implementation plan. Evolving from a traditional to consumer-centric care model is a stepwise process that requires careful monitoring of what works to manage safety concerns, to facilitate adoption, and to align stakeholder interests. We characterize five stages of activity relevant to our ongoing internal implementation of PHM (Table 2). Each stage is differentiated by its primary objective, its scale, its primary outcomes, and its relevance to the business of delivering care.

The steps in our implementation plan represent a research and development-like model in which there is a progression from proof-of-concept to marketable product. Tactically, the process for any stage of work invariably involves a consideration of the business case (i.e., the potential for a meaningful ROI), management of stakeholder engagement, content creation, workflow re-design, translation of content into actionable specifications, implementation, and evaluation. Each of these steps is quite complex and common to any process redesign. Our focus in this section is on the broader stages of work, not the tactical steps common to any redesign effort.



Progression through the above stages requires that the process and/or tool meet certain requirements. Stage 1a is focused on proof of concept. Proof of concept has necessarily been a dominant activity over the past two years and will continue to be for the foreseeable future. Expectedly, many more concepts are tested in Stage 1a than succeed and progress to subsequent stages. Although nearly all new product development efforts are ultimately motivated by the potential for a meaningful return on investment (ROI), our Stage 1a and 1b development and testing efforts are not focused on either measuring or achieving a positive ROI. Rather, they are focused on rapid feedback and learning while developing a functional model for use in daily care (Stage 1a) and developing a process and/or tools that are deemed acceptable by patients and providers (Stage 1b). For both first and second stage activities, testing is usually limited to one or a few clinics and can range from a new system of care (e.g., medical home) to testing of new tools (e.g., patient data capture tool, visual display tool, clinical decision support tool) or

<b>Table 2. Stages in development and deployment of new care processes</b>				
<b>Stage</b>	<b>Primary Objective</b>	<b>Scale</b>	<b>Outcomes<sup>1</sup></b>	<b>Business Considerations</b>
1a	Proof of concept for prototype	One to two clinic patient populations	Functionality of process, tools, patient satisfaction	Theory of ROI and associated metrics
1b	Proof of value for prototype	One to two clinic patient populations	Patient acceptability and satisfaction, early quality and efficiency of care, efficiency of care, acceptability by providers	Evidence of potential for ROI
2	Proof of value with the scalable prototype	Multiple clinics populations, using quasi-experimental design	Quality of care, use of care, continuity of care, efficiency of care	Documented ROI
3	System level (single focus) implementation to increase customer growth and competitive advantage	System level implementation within a domain, IT ownership of processes, and re-organization of clinic space	Seamless integration, documentation of increased productivity for the same provider effort, improvement in patient outcomes and reduced need for care. Reduced cost to consumer per unit gain in outcome. Reliable use and process performance across diverse settings	Sustainable increase in net revenues through greater RVUs/time and documentation of work done Sustainable PMPM savings
4	Performance improvement and diversification of processes/tools to other clinical domains and settings	System level	Patient data capture, CDS, education and care planning/oversight happen as part of routine care	Continued increase in net revenues, decrease in PMPM. Collaborative work with payors
5	Export capabilities to other systems and markets	Market Level	External market purchase of consulting, processes, tools, etc	New ventures, partnerships or licensing activities

<sup>1</sup> – A key outcome across all stages is the extent to which consumer interactions are increasingly semi-virtual to virtual

processes. We distinguish proof of concept, which is largely focused on developing a workable model, from initial validation of proof of value (Stage 2). In our experience, there are two reasons why it is not usually sensible to simultaneously evaluate functional proof of concept and proof of value. First, simply developing and testing new processes is complex and consumes enormous resources, as the new process has to be seamlessly integrated with the existing workflows and practice settings. Second, because there are usually so many lessons learned in the first stage, the prototype version used in the second stage (i.e., proof of value) may differ substantially from first stage testing. The value proposition may also change, making the first

stage value proposition irrelevant. Second stage work is worth pursuing when feedback from all stakeholders (i.e., patients, providers, clinic staff, etc) indicates that the model is workable and offers potential value.

Stages 3 and 4 represent a fundamental shift in emphasis and responsibility. Initiating Stage 3 work only occurs when executive leadership is convinced that proof of value is established, that safety issues have been fully addressed, and that translation of the prototype to a system level operation is feasible and desirable. This critical step represents an important transition to relying on external funding (e.g., research) and modest amounts of internal funding to a more significant system level investment in infrastructure. Moreover, executive support also means an important shift in IT emphasis and control from research and innovations testing in a secure environment to control by the system level IT department for broader implementation, management and ongoing support. Finally, we note that stage 5 represents a very different type of shift in emphasis and control from one that is internally focused to one that explores commercialization opportunities in the commercial market. Stage 5 work involves the collaboration among venture capital experts, system level IT leaders, and other experts to develop a more generalized solution for diverse environments and to evaluate market opportunities.

In our recent experience, activity relevant to any one stage creates feedback loops to other stages. Expectedly, the accumulation of lessons learned creates a valuable organizational asset. Moreover, tools developed for different projects are combined to create new processes. Over time, we expect an acceleration of new developments that leverage earlier stage 1 and 2 work. Based on work over the past two years, it is clear that experience in developing and testing new processes and tools in one setting, lead to accelerated application of proven prototypes in other areas, reducing the need for Stage 1 testing and possibly Stage 2 testing of a similar process or tool in a different clinical area. We consider two specific examples of this type of evolution in research and development.

- We are creating a second generation semi-automated cardiovascular disease (CVD) risk management system for primary care that identifies data needs, quantifies patient risk, engages patients at elevated risk in a decision process, and informs the clinician of consumer choice and expert advice (automated decision support). This system is actually the product of work over the past three years focused on testing patient data capture tools (i.e., Stage 1a) using various technologies in a variety of settings, a cardiovascular risk calculator that will soon be used in primary care, and an early version of an interactive decision support/preference elicitation tool for consumers. This work on CVD risk management has provided the foundation for parallel developments of a diabetes disease management process for primary care. This represents an example of leveraging previous work to bypass one stage (i.e., 1a) of work, moving directly to the subsequent stage (i.e., 1b). The diabetes project leverages many of the developments for the CVD project and, in our view, represents what is likely to unfold in a number of areas.
- Development of a rheumatology practice system that captures outcomes data from patients during each visit, provides an integrated and intuitive on-demand display of all patient data (i.e., labs, clinical, functioning, pain, etc), and automatically drafts structured progress notes and a patient after-visit summary. Again, development of this process is based on several years of work, borrowing from experience in the development of other tools. The visual display tool is being developed to function in a web environment but to also interact with our

EHR. We expect to apply this same type of process (i.e., patient data capture and interactive visual display tool) to other specialty care areas where information needs are complex (e.g., oncology), and time is too limited to carefully review all data during a given encounter. Moreover, development of tools in a web environment is deliberate, as it provides the foundation for possible use in other settings outside of Geisinger whether or not an EHR is available.

Space does not allow us to fully describe our expectations over the next five calendar years (2009 – 2013) for all clinical care settings (i.e., primary care, specialty care, surgery, inpatient care, home care, end of life care). Instead, Table 3 offers a specific profile of how each PHM objective will be addressed over the next five years in primary care. This profile represents our limited view based on recent experience and will necessarily evolve with growth in experience and lessons learned. While representative, the table itself is incomplete, as not all developments currently underway are represented and others are likely to be added. As previously noted, PHM related work has been under way at Geisinger over the past three years. Specifically, we have been engaged in the ongoing development and implementation of an enterprise-wide data warehouse. While this warehouse is not currently interoperable for real time use, it provides the foundation for future implementation of this type of process. Future work will involve incorporation of existing databases that are not currently accessible in real time and, more generally, the incorporation of other types of “data” resources, including questionnaire protocols, highly tailored clinical rules and related text content, libraries of community resources that are relevant to supporting consumers where they reside. Virtual and semi-virtual encounters will depend on the evolution of access channels in traditional settings as well as at home or under other conditions (e.g., from work). We have gained extensive experience in developing patient data capture tools and developing workflows to support their use in practice. Over the next five years, the creation and implementation of PARDAMS will dominate our work in this arena and foster parallel evolution in implementing protocols for consumer choice processes, provider CDS, and shared decision making. Operationally, there is a strong interdependence among the processes relevant to these four objectives.

We note that the processes and tools that we develop for future application will have to be nuanced to the features of the population of interest. Tools will differ depending on the clinical setting. We expect that sophisticated interactive visual dashboards will be more important in specialty care than in primary care. On the other hand, automated real time actionable CDS that is highly nuanced to the encounter and a given consumer will be fundamentally important to PHM in primary care. The focus of interest in development of tools and processes will, of course, also differ by the health care setting, as well by other broadly defined categories of health problems (e.g., pediatric ENT, end-of-life care) and diseases (e.g., oncology) and conditions. For inpatient care, we expect a strong focus on creating reliable, consistent, and integrated means of managing care transitions. In primary care, the process for chronic episodic conditions (e.g., migraine, depression, asthma, low back pain, GERD, bladder control, etc) will involve integration of sophisticated questionnaires, consumer preference menus, CDS, and periodic asynchronous evaluation of outcomes status. As described above, the process and tools differs to some degree for managing chronic progressive disorders. With experience, we expect that a market focus will play an increasingly important role in identifying new opportunities that offer a meaningful return on investment in new tools and processes.

## **CONCLUSIONS**

In 2007, healthcare expenditures in the US were approximately 2.3 trillion dollars (2). Despite the enormity of this outlay, the collective return on our national investment is unclear: costs continue to rise, millions remain uninsured, and the quality of care remains suboptimal. Our vision of a healthcare system that places the patient – acting as a consumer, but supported by intelligent tools and a receptive care delivery system – at the center of the care process is the primary requirement of this necessary cultural shift to Personal Health Management.

One can reasonably argue that our vision for PHM fails to consider the complexities of the healthcare system. However, consistent with the eventual disproof that the decision making required for non-healthcare interactions is too complex to be enabled by interactive computer-mediated encounters (e.g., social match-making, financial portfolio management, travel scheduling, etc.), we predict that the PHM model is inevitable.

A primary potential benefit of the PHM approach is that as more consumers become more engaged, there are a large number of health-enhancing behaviors that are likely to be adopted that would never have a chance in a passive “what comes, will come” attitude and approach that primarily exists today. Such innovation is sorely needed as we seek to enable individual consumers while simultaneously having a positive sustainable population-level impact on the chronic disease epidemic afflicting our nation.

<b>Table 3. Implementation expectations at Geisinger over the next five years for Primary Care Practices</b>										
PHM OBJECTIVE	<b>PHM Stage (<i>St</i>) of implementation and focus of work by care setting and calendar year</b>									
	<b>2009</b>		<b>2010</b>		<b>2011</b>		<b>2012</b>		<b>2013</b>	
	<b><i>St</i></b>	<b>Focus of Work</b>	<b><i>St</i></b>	<b>Focus of Work</b>	<b><i>St</i></b>	<b>Focus of Work</b>	<b><i>St</i></b>	<b>Focus of Work</b>	<b><i>St</i></b>	<b>Focus of Work</b>
Interoperable Data Warehouse	3	Phase I implementation of data critical to day to day operations	3	Addition of non-EHR clinical data captured in other devices	3 & 4	Addition of questionnaires, clinical rules, and CDS databases for most common conditions	3 & 4	Expansion of questionnaires, clinical rules, and CDS databases for other conditions and addition of GIS based community resources	3 & 4	Expansion of questionnaires, clinical rules, and CDS databases for other conditions
Access Channels	3 & 4	MyGeisinger web portal for record review, Rx orders, scheduling, communication, etc. with provider	1A	Home based encounters with patient using an online interactive tool and phone consultation. Expand use of computer touch screens in clinics	1B	Home based encounters with patient using an online interactive tool and phone consultation. Re-organize waiting areas to patient working areas	2	Home based encounters with patient using an online interactive tool and synchronous or asynchronous interactions with provider	3	Home based encounters with patient using an online interactive tool and synchronous or asynchronous interactions with provider
Consumer Data	1B	Test proof of value of questionnaires for selected common conditions and utilities (e.g., medication reconciliation)	2	Develop a scalable model with expansion of types and uses of questionnaires for in-clinic patient data capture. Continue ROI evaluation	3	System level implementation of patient data capture processor for in-clinic data capture and remote data capture	4	Expand library of questionnaires and access channels	4 & 5	Expand library of questionnaires and access channels. Commercialize questionnaire product
Consumer Choice	1A	Continue pilot testing and re-engineering preference based care tools for common conditions	1B	Evaluate proof of value of preference based care tool for patient outcomes and clinical ROI.	2	Develop, deploy, and evaluate scalable version of preference based care tool	3	Deploy system level tool for routine use of preference based care tool	4 & 5	Expand libraries of tool interfaces for multiple conditions and expand use to external market
Provider Support	1A	CDS modules to provide real time expert guidance at the point of care for CVD, diabetes, headache	1B	CDS modules to provide real time expert guidance at the point of care for CVD, diabetes, headache. Integrate visual display tool with CDS	2	Testing of prototype system level tool that manages libraries of expert knowledge for multiple conditions and related visual displays. Test automated problem list manager.	3	Implement system level tool that manages libraries of expert knowledge for multiple conditions per prototype in 2011	4	Continued expansion of libraries of expert knowledge for multiple conditions
Shared Decision Making	1A	Proof of principles for linking alert in EHR to web application that displays patient preferences and decisions	1B	Proof of value for prototype model that links an alert in EHR to web applications that displays patient preferences and decisions	2	Integration of consumer data, consumer choice, and provider support to improve SDM process	3	System level integration of consumer data, consumer choice, and provider support to improve SDM process	4 & 5	System level expansion of conditions covered through integration of consumer data, consumer choice, and provider support to improve SDM process. Evaluate market opportunity.
Continuous Management					2	Test prototype models for semi-automated and automated continuous care management in several clinical areas	3	System level version of model for semi-automated and automated continuous care management for use in several clinical areas	4	System level version of model for semi-automated and automated continuous care management for use in an expanded number of clinical areas

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# Role of Professional and Medical Specialty Societies in the Era of Personalized Health Practice

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## US Cost and Quality Challenges: The Context for Personalized Health Care

Similar to the precarious positioning of Odysseus' ship between the dangers of Scylla and Charybdis,<sup>1</sup> it is well documented that health care is currently caught between two pressures: demand for improved health outcomes and quality and constraints on the spending required to deliver on these improvements.<sup>2,3,4</sup> Successful cost reduction strategies may sacrifice quality. Alternatively, strategies to increase quality may result in excessive system costs. Striking the appropriate balance between these two forces is likely be the best means to overcome the challenges facing our United States (US) health system.

Growth in US health spending hovers at 7% per year, double-digit increases in annual insurance premiums have occurred in many recent years, and overall health expenditures are anticipated to double in under a decade.<sup>5,6</sup> These trends are viewed by many health

<sup>1</sup> Scylla and Charybdis are two monsters from Greek Mythology viewed as virtually impossible for ships to pass between, as getting too close to either risked destruction of the crew and ship.

<sup>2</sup> Califf RM. Defining the balance of risk and benefit in the era of genomics and proteomics. *Health Affairs*. 2004;23(1):77-87.

<sup>3</sup> Faulkner E. Addressing the realities of health care in the 21st century: a time for collaborative solutions. *J Manag Care Med* 2005;(8)2:11-2.

<sup>4</sup> Gelijns AC, Brown L, Magnell C et al. Evidence, politics, and technological change. *Health Affairs*. 2005;24(1):29-40.

<sup>5</sup> Ibid.

<sup>6</sup> Employer Health Benefits 2007 Annual Survey. Kaiser Family Foundation 2007.



policy and decision makers as unsustainable long term.<sup>7,8</sup> Such trends in health spending have increasingly forced payers, providers, employers, and patients to explore less costly means for achieving high-quality care and maintaining sustainable health care delivery models.

A variety of factors influence the increase in health care spending in the US. Key factors include but are not limited to the aging population, increasing prevalence of chronic diseases, inappropriate use of health services and stakeholder incentives, inefficient health delivery systems, focus on treating sickness versus promoting wellness, and the expansion of emerging health technologies. These factors are complex, intimately intertwined and when taken in the context of our highly fragmented health delivery system, make health reform in the US a daunting prospect.

The US Congressional Budget Office (CBO), Institute of Medicine (IOM) and other influential groups have cited the availability of innovative and breakthrough health care technologies and lack of clarity surrounding their use as a significant driver of increased health care spending.<sup>9,10</sup> On the other hand, new health technologies can often enable sophisticated, effective, and increasingly personalized care.<sup>11,12</sup> Some technologies, such as molecular diagnostics and targeted treatments promise to alter paradigms of care and optimize individual health outcomes, pending real world validation in clinical practice.<sup>13</sup> Balancing affordability of new health technologies against innovation and opportunities for care enhancement will prove challenging in an era of tightening budgets and increased health services utilization constraints.

Just as new health technologies may improve health quality and distribution of costs, evolving health information technology (HIT) and decision support systems<sup>14</sup> promise efficiencies in health services delivery. However, adoption of information systems in

<sup>7</sup> Health care spending in the United States and OCED countries. Kaiser Family Foundation 2007.

<http://www.kff.org/insurance/snapshot/chcm010307oth.cfm>.

<sup>8</sup> National health expenditure projections 2007-2017. National Health Expenditures Survey. Centers for Medicare and Medicaid Services 2007. <http://www.cms.hhs.gov/NationalHealthExpendData/Downloads/proj2007.pdf>.

<sup>9</sup> Technological change and the growth of health care spending. U.S. Congressional Budget Office. January 2008

<sup>10</sup> Knowing what works in health care: a roadmap for the nation. Institute of Medicine. National Academy of Sciences 2008.

<sup>11</sup> The value of diagnostics: innovation, adoption and diffusion into health care. Advanced Medical Technology Association. Jul 2005.

<sup>12</sup> Cutler DM, Rosen AB, Vijan S. The value of medical spending in the United States, 1960-2000. NEJM 2006: 355(9).

<sup>13</sup> Realizing the Potential of Pharmacogenomics: Opportunities and Challenges. Secretary's Advisory Committee on Genetics Health and Society 2007. [http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS\\_PGx\\_Report.pdf](http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_Report.pdf)

<sup>14</sup> Decision support systems references a broad variety of software-based systems that aim to improve end user (in this case physicians and other clinical decision makers) decision making by synthesizing, simplifying and/or involving algorithms that facilitate manipulation of complex or potentially confusing information.

health care has lagged behind other industries due to lack of information standards, limited systems interoperability or information sharing, insufficient financial incentives and other factors.<sup>15</sup> For example, the retail industry (e.g., large department store chains such as Walmart or Target), financial services industry (e.g., banking and investments), and shipping industry (e.g., Federal Express and United Parcel Service) gain significant operational efficiencies via reliance on highly sophisticated information systems. Likewise, clinical decision support systems must evolve considerably to offer solutions relevant to day-to-day decision needs of care providers. In the near future, mandatory and voluntary government and commercial initiatives focused on clinical best practices, quality improvement, and health care transparency will increase the desire for application of HIT to improve provider operations and compliance with expanding data collection and reporting requirements.<sup>16</sup>

Personalizing and better targeting care practices based upon individual needs and health indicators is one possible solution to help defray growing cost and quality challenges. On September 19, 2007, the US Department of Health and Human Services (HHS) Secretary Michael O. Leavitt unveiled the forward looking report entitled *Personalized Health Care: Opportunities, Pathways, Resources*.<sup>17</sup> This “early reconnoitering” report lays a conceptual roadmap for harnessing our rapidly expanding biomedical knowledge base and health information systems to enable increasingly personalized health care.

The concept of personalized health care is very broad, integrating our growing knowledge of genetics and biomarkers and their role in treatment selection with HIT, principles of evidence-based practice, and health quality and performance improvement approaches. In essence, personalized health care would combine the best available information from a variety of sources in an actionable manner so that physicians and patients can make appropriate health care decisions and enhance use of individual patient data in health practice.<sup>18</sup> Despite the intuitive appeal of personalized health care, successful implementation will not occur effectively without deliberative forethought and the collaborative engagement of many health stakeholders.

The focus of this paper is to explore what would need to happen for medical and scientific specialty societies (professional societies) to assume a lead role in enabling delivery of personalized health care that leverages knowledge of individual variability.<sup>19</sup>

<sup>15</sup> Overcoming barriers to electronic health record adoption. Health Care Financial Management Association 2006. [http://www.hhs.gov/healthit/ahic/materials/meeting03/ehr/HFMA\\_OvercomingBarriers.pdf](http://www.hhs.gov/healthit/ahic/materials/meeting03/ehr/HFMA_OvercomingBarriers.pdf)

<sup>16</sup> Based on objectives defined in the Medicare Prescription Drug, Improvement and Modernization Act (MMA) of 2003 and other initiatives focused on health care quality and performance improvement.

<sup>17</sup> Personalized Health Care. Opportunities, Pathways, Resources. United States Department of Health and Human Services. 2007. Accessed September 28, 2007: <http://www.hhs.gov/myhealthcare/news/phc-report.pdf>.

<sup>18</sup> Faulkner E. The road to value-based healthcare: destination apparent, journey uncertain. *J Manag Care Med* 2006;(9)3:27-9.

<sup>19</sup> The US Department of Health and Human Services (HHS), Office of the Assistant Secretary for Planning and Evaluation (ASPE) has commissioned this white paper as one in a series intended to evaluate and conceptualize business and management processes necessary for integration of personalized medical practices into health care.

Understanding drivers and incentives of relevant stakeholders will also be important to comprehensive strategies for personalized health care (see Appendix A). More broadly, this paper considers issues relevant to the collaboration among key stakeholders around personalized health care issues, as well as business and operational implications of these factors for professional societies.

### **Balancing Standardized vs. Personalized Health Care**

In some respects, personalized health care approaches may run contrary to or even disrupt health care paradigms centered on standardizing clinical practice and delivery. Further, existing policies, business incentives, and decision drivers, such as those outlined below, may hinder implementation of personalized health care solutions in the US. The following section highlights some basic challenges of balancing standardized versus personalized health care; this overview provides a foundation for discussion of how professional societies may play a leadership role in implementing personalized health practices.

**Considerations for evidence-based practice and policy:** Evidence-based medicine (EBM) emphasizes using the best available clinical (and often economic) evidence to inform the appropriate use of new health technologies. Evidence-based approaches attempt to link risks and benefits of the intervention to patient outcomes and quality-of-life improvements using a process called health technology assessment (HTA).<sup>20</sup> HTA synthesizes evidence from existing studies to characterize the value of a diagnostic or treatment in the context of clinical practice.

As knowledge linking individual patient information to disease risk and treatment outcomes grows in the coming years, evidence-based policies and guidelines geared largely toward standardizing care approaches for broader patient populations will have to adapt in tandem. Likewise, approaches to evidence assessment (e.g., HTA practices, data modeling) and decision support will also become increasingly necessary to address an expanding evidence-base that incorporates personalized health care information. While there is no doubt that personalized health care will be beneficial in many ways, we are only beginning to realize the implications that knowledge of individual variability confers.

These efforts also address issues central to the forward-looking aspects of Secretary Michael Leavitt's Personalized Health Care Initiative that emphasize planning for the integration of personalized health principles into the delivery of health care. By identifying barriers to personalized health care and best practices to overcome them, HHS will be better prepared to communicate and plan for health systems change in a manner that appropriately leverages new technology and medical innovation, supports viable financial models, and engenders highly efficient, quality-focused, and personalized health care delivery practices.

<sup>20</sup> Elstein AS. On the origins and development of evidence-based medicine and medical decision making. *Inflamm. Res.* 53 Suppl (2) 2004: S184–9.

Personalization of health care will vary depending upon the potential for individualization of treatment. For example, our ability to leverage biomarker-related patient management may differ by health condition (e.g., allergic rhinitis, diabetes, psychological conditions and cancer) and other factors (e.g., correlation of genotype to phenotype, ability to intervene based on biomarker information, involvement of single versus multiple genes). While evidence-based practice has always taken into account individual variability and subpopulation effects, it is clear that the magnitude and frequency of new clinically relevant information based on genomics-related knowledge will challenge our existing processes for translating knowledge into practice.

Movement towards personalized health care raises several broader considerations for evidence-based practice and policy, including but not limited to the following.<sup>21,22,23</sup>

- Under which scenarios are evidence-based standardized approaches or personalized approaches most beneficial, practical, and cost-effective? What are our limitations for personalizing health care?
- How does expansion of personalized health information influence prioritization of topics for HTA given limited funding for such endeavors? Should additional focus in this area be facilitated and in what ways?
- How should HTA processes change in regard to the timing of evaluations, definitions of ideal or acceptable evidence (e.g., evidence from models or longitudinal databases versus randomized controlled trials), and resultant recommendations for use?
- How will personalized health care models influence sponsor evidence requirements for securing market clearance and reimbursement? Will this diminish or enhance incentives for innovation and availability of new health technologies?
- What are the implications of increasingly complex treatment scenarios and decision steps for clinical guideline development and maintenance?
- How will personalized health information be communicated in a manner useful to policy makers, payers, providers, and patients?
- How and in what ways will complex individual health information be practically implemented into existing patient management and health decision frameworks?
- Which stakeholders will pay for the complex and costly data collection

<sup>21</sup> Clancy, C. The evolution of evidence-based medicine and personalized healthcare. Presented at the 21<sup>st</sup> Century Medicine: Personalized and Evidence-Based conference. Washington, DC 2007.

<sup>22</sup> Khoury MJ, Gwinn M, Burke W, Bowen S, Zimmern R. Will genomics widen or help heal the schism between medicine and public health? *Am J Prev Med.* 2007;33(4):310-7.

<sup>23</sup> Developing Biomarker-based Tools for Cancer Screening, Diagnosis and Treatment. IOM Workshop Summary 2006.

and analysis that may be applicable to personalized health practice? Who will distinguish “got to have” vs. “nice to know” evidence requirements?

- How much emphasis on personalization in health practice is too much (i.e., where the costs of personalized treatment outweigh the value of standardization and population-based approaches)?

Inefficient integration of evidence-based medicine and personalized health care practices may:

- Inappropriately preclude access to beneficial health technologies
- Create overburdensome evidence development requirements
- Involve unnecessary health data collection and reporting requirements, and
- Challenge existing health care business models.<sup>24,25</sup>

On the other hand, appropriate personalized health policies and practices offer the potential to avoid adverse health outcomes associated with unclear treatment scenarios, increase the precision of care management, and redirect expenditures towards health quality and efficiency gains.<sup>26</sup> Addressing relevant questions and sketching viable knowledge translation and health delivery frameworks will be essential to fully realize the promise of personalized health care and adapt existing approaches, as appropriate, to balance standardized and personalized care.

**Considerations for health quality and performance management:** Health quality measures, just like clinical practice guidelines, are evidence-based and focus on characterizing standards of clinical practice and patient care. Such quality measures are often very specific (e.g., measurement of a diabetic patient’s HbA1c every 6 months) with years of evidence that support the measure as a standard of care. At baseline, health quality measures must be measurable and used in instances where the desired change in health delivery is achievable .

Health quality measures are increasingly used in evolving pay-for-performance (P4P) programs. Quality-measure-driven P4P programs provide financial incentives to hospitals or individual physicians for providing health care services as defined under performance management contracts and often involve “dashboards” of quality measures that characterize various aspects of provider performance. In fact, quality measures are increasingly based on clinical practice guidelines, providing additional incentives for hospitals and physicians to follow established standard care practices and extending the influence of evidence-based practice in all aspects of care.

<sup>24</sup> Gwinn M, Khoury MJ. Genomics and public health in the United States: signposts on the translation highway. *Community Genet* 2006;9(1):21-6.

<sup>25</sup> Garrison LP and Austin MJF. Linking pharmacogenetics-based diagnostics and drugs for personalized medicine. *Health Affairs* 2006;25(5):1281-1290.

<sup>26</sup> Ibid.

The Centers for Medicare and Medicaid Services (CMS), commercial managed care organizations (MCO), and large employers/employer coalitions have experimented extensively with quality management and P4P approaches for almost a decade. Although results in the US health system have been mixed and best practices are still evolving, quality improvement and P4P programs are here to stay.<sup>27,28,29</sup> In general, these programs are intended to support good clinical and operational approaches and increase the consistent provision of accepted practices in areas with notable and actionable inefficiencies.<sup>30</sup> In the near future, quality and information reporting requirements under CMS and other programs such as the Reporting Hospital Quality Data for Annual Payment Update (RHQDAPU) and the Physician Quality Reporting Initiative (PQRI) will significantly expand collection of quality-related data and accelerate evolution of P4P.<sup>31</sup>

At present, the implications of personalized health care for quality measurement and P4P paradigms is uncertain and has not been well studied. As these programs evolve from broader foci (e.g., inpatient quality, outpatient quality) towards practice- or disease-specific quality measures, there is greater potential for emphasis on individual variability. However, current clinical practice guidelines often lack the specificity for development of quality measures or decision support systems (even without introduction of individual variability). On one hand, system incentives should not be structured in a manner that diminishes individualized health approaches, targeted technology applications, and innovation. On the other hand, integration of personalized health practice should not occur in a manner that rejects the value of standardization and creates unnecessary administrative and financial burdens for health stakeholders.

**Considerations for business and operational efficiency:** In the short term, as the tools for personalized health care evolve, processes for integration will be subject to uncertainty as we gain familiarity and confidence in applying individual health information. Health decision makers must also weigh applicability of current policies and practices where decisions may be made on a variable scenario-by-scenario basis.<sup>32</sup> Business integration challenges will center on both the cost and efficiency of care as health delivery continues to shift towards preventive and individualized care.

<sup>27</sup> Glickman SW, Ou FS, DeLong ER, et al. Pay for performance, quality of care, and outcomes in acute myocardial infarction. *JAMA*. 2007;297(21):2373-80.

<sup>28</sup> Tanne JH. Performance related pay doesn't improve quality of primary care, US study finds. *BMJ*. 2008;337:a1160

<sup>29</sup> Linares A, Gauthier P, Isaacs C, Barnett P, et al. The benefits of pay-for-performance programs are worth the cost and hassles to provider organizations to participate. *Health Data Manag* 2007;15(12):10.

<sup>30</sup> McGlynn EA, Asch SM, Adams J, Keesey J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med* 2003;348(26):2635-45.

<sup>31</sup> Stulberg J. The physician quality reporting initiative--a gateway to pay for performance: what every health care professional should know. *Qual Manag Health Care* 2008;17(1):2-8.

<sup>32</sup> Ferrara J. Personalized medicine: challenging pharmaceutical and diagnostic company business models. *MJM* 2007;10(1): 59-61.

The expansion of biologics and targeted therapies is illustrative of the opportunities and challenges associated with transition to personalized health practice. In 2005 there were approximately 350 biologics in phase III trials or undergoing FDA review, and over 2,000 others are in early development.<sup>33</sup> A recent study of Blue Cross Blue Shield plans reported that spending on specialty pharma products has risen almost 35% between 2002 and 2003, and these products are estimated to represent 25% of all outpatient pharmacy spending by 2008.<sup>34,35,36</sup> As the cost to patients of some specialty pharma products approaches or exceeds \$10,000 per month, overall affordability and access are key considerations for US health care, despite the potential value of such treatments.<sup>37</sup> While some of these products may markedly improve mortality and quality of life through targeted treatment, others will only offer marginal benefits—because of these scenarios, value assessment is important for informed treatment utilization and sustained access.

Likewise, emerging molecular diagnostics (e.g., gene/protein expression or array-based diagnostics, multi-biomarker panels, gene sequencing tests) show great promise for increasing the effectiveness and individualization of care. Diagnostics may also enable avoidance of certain downstream costs and patient adverse events/complications by informing more sophisticated early decision making and intervention/treatment strategies. Despite this promise, US MCOs have voiced concern because some new molecular diagnostics are priced significantly higher than predecessor diagnostics (generally priced in the 10s to 100s of dollars), with price ranges approaching \$4,000 per test.<sup>38,39</sup> As a result and with a host of similar and costly tests in development, payers and federally supported efforts such as Evaluation of Genomic Applications in Practice and Prevention (EGAPP) are moving to develop HTA processes, decision criteria, and management practices that consider the unique attributes of diagnostics and implications for personalized health practice.<sup>40,41,42</sup>

<sup>33</sup> Watkins JB, Choudhury SR, Wong E, Sullivan SD. Managing biotechnology in a network-model health Plan: a US private payer perspective. *Health Affairs* 2007;25(5):1347-52.

<sup>34</sup> Mullins CD, Lavalley DC, Pradel FG, et al. Health plans' strategies for managing outpatient specialty pharmaceuticals. *Health Aff* 2006;25(5):1332-9.

<sup>35</sup> Ibid.

<sup>36</sup> Stern D, Reissman D. Specialty pharmacy cost management strategies of private health care payers. *J Manag Care Pharm.* 2006;12(9):736-44.

<sup>37</sup> Fish L. The case for cost sharing for biologic therapies. *Amer J Manag Care* 2006;12(6):159-161.

<sup>38</sup> OncoType Dx. Wikipedia 2008. Accessed on August 15, 2008 at: [http://en.wikipedia.org/wiki/Oncotype\\_DX](http://en.wikipedia.org/wiki/Oncotype_DX).

<sup>39</sup> When new technology revolutionizes patient care: a blood test that provides new information about transplant rejection. *Executive Healthcare Management* 2008. Accessed on August 15, 2008 at: <http://www.executivehm.com/pastissue/article.asp?art=270586&issue=210>.

<sup>40</sup> About EGAPP. National Office of Public Health Genomics. Centers for Disease Control and Prevention. <http://www.cdc.gov/genomics/gtesting/EGAPP/about.htm>.

<sup>41</sup> Diagnostics have historically represented only approximately 2-3% of overall US health expenditures and have not until recently garnered significant concern from payers and policy makers. <http://www.socalbio.org/pdfs/thevalueofdiagnostics.pdf>

<sup>42</sup> Bell G. Managing office administered drugs: an economist's perspective. *JMCM* 10(2) 2007.

New health technologies have catalyzed a host of cost and utilization management strategies relevant to payers and providers, including but not limited to the approaches presented in Table 1. It will be important to consider “fit” of personalized health practices within this complex system of cost controls and the policies guiding their use.

**Table 1. Cost Containment Strategies for New Health Technologies**

Coverage	Utilization	Health Plan Rules	Cost Sharing
<ul style="list-style-type: none"> <li>• Benefit exclusions</li> <li>• Denials not subject to appeal</li> <li>• Noncoverage because the product is deemed investigational or experimental</li> <li>• Conditional coverage</li> <li>• Value-based purchasing</li> <li>• Data mining to refine coverage</li> <li>• Exclusion of certain drugs/drug classes from coverage</li> </ul>	<ul style="list-style-type: none"> <li>• Specialty drug limits</li> <li>• Disease limits/disease management models</li> <li>• Coverage for label use only</li> <li>• Retrospective utilization review</li> <li>• Health care transparency and data reporting</li> <li>• Provider profiling</li> <li>• Dispensing limits</li> </ul>	<ul style="list-style-type: none"> <li>• Step therapy</li> <li>• Prior authorization</li> <li>• Mandatory generic substitution</li> <li>• Pay for performance</li> <li>• Closed formulary</li> </ul>	<ul style="list-style-type: none"> <li>• Coinsurance</li> <li>• Copay models</li> <li>• New formulary tier strategies</li> <li>• Deductibles and out of pocket maximum payments</li> <li>• Lifetime maximum payments</li> <li>• Reference pricing</li> <li>• Risk sharing and rebates</li> </ul>

Adapted from: Hoadley J. Cost containment strategies for prescription drugs. Kaiser Family Foundation report, March 2006 and Cost-containment Strategies for Prescription Drugs. Kaiser Family Foundation. 2005; Morrow T. Biopharmaceuticals: the view of the future BIO 2005 breakout session.

Increasing health data collection and reporting requirements of public and commercial payers also place financial and operational pressures on hospitals, physician practices, and other providers.<sup>43,44,45</sup> These efforts, intended to improve health quality and cost control, include pilot and other programs covering multiple care settings and include an increasing array of information related to quality of care (e.g., longitudinal health databases and patient registries), provider performance, and use of health services and technologies. While national provider adoption of electronic health records, data capture

<sup>43</sup> Reporting hospital quality data for annual payment update. Centers for Medicare and Medicaid Services. [www.cms.gov](http://www.cms.gov).

<sup>44</sup> CMS increasing required data reporting. Brigham and Women’s Hospital. Accessed August 15, 2008 at: <http://www.brighamandwomens.org/publicaffairs/publications/DisplayMSN.aspx?articleid=1614&issueDate=11/1/2007%2012:00:00%20AM>.

<sup>45</sup> US Department of Health and Human Services Medicare hospital value-based purchasing plan development. Centers for Medicare and Medicaid Services 2007. [http://www.cms.hhs.gov/AcuteInpatientPPS/downloads/hospital\\_VBP\\_plan\\_issues\\_paper.pdf](http://www.cms.hhs.gov/AcuteInpatientPPS/downloads/hospital_VBP_plan_issues_paper.pdf).



systems, and information technology remains low (~23%-27%), broader adoption would be a necessary prerequisite for personalized health care.<sup>46</sup>

At present, while data on individual patient variability (e.g., diagnostic test information) is included in some data reporting initiatives, there is not yet a comprehensive data reporting approach centered on personalized medicine or personalized health care. Recently introduced bills (S.3822, the Genomics and Personalized Medicine Act of 2006 and H.R.1321, the Medicare Advanced Laboratory Diagnostics Act of 2007) would incorporate data reporting elements, but are unclear regarding incentives for providers, diagnostics manufacturers, reference laboratories, and other stakeholders that would defray the costs associated with data reporting, database maintenance, and data access or analysis.

Integration of HIT certainly holds great potential for improving health care efficiency, quality, and cost, but must also be balanced against the practical business and operational impacts on key health stakeholders. Integration of HIT is one important component of the ability to offer personalized health care, but well-developed provider organizations driven by appropriate system incentives and underpinned by organizational supports and systems also will be necessary to support personalized health care across the diverse array of provider organizations in the US.

The aforementioned considerations are a modest sample of the policy, business, and translational issues associated with integration of personalized health practices with established and standardized health delivery models. They are, however, illustrative of the complex challenges facing those involved in health care reform and in efforts supporting the transition to personalized health care. The remainder of this paper will consider elements necessary for professional societies to play a leadership role in evolution of personalized health practice, given the pressures and implementation issues presented.

### **How Professional Societies Can Contribute to Elements Important to Personalized Health Care**

There are hundreds of scientific and clinical specialty and other societies (professional societies) in the US that may be relevant to advancement of personalized health care. Each professional society has its own mission and vision, unique focus, and range of service offerings that are relevant to members and external stakeholders. Professional societies offer great value to the health care field by serving a myriad of functions, including but not limited to continuing medical education; development of clinical practice guidelines; informing health policies and practice standards; refining research standards, decision tools and business practices; and serving as a venue for health stakeholder collaboration and communication.

<sup>46</sup> Ibid.

For purposes of this paper, societies relevant to the support and advancement of personalized health care would fall into the general categories identified in Table 2.

**Table 2: Types of Professional and Medical Specialty Societies Relevant to Personalized Health Care**

Category	Example Organizations
Medical specialty societies	<ul style="list-style-type: none"> <li>• American College of Cardiology (ACC)</li> <li>• American College of Rheumatology (ACR)</li> <li>• American Psychiatric Association (APA)</li> <li>• American Society of Clinical Oncology (ASCO)</li> </ul>
Medical professional and health management societies	<ul style="list-style-type: none"> <li>• Academy of Managed Care Pharmacy (AMCP)</li> <li>• America’s Health Insurance Plans (AHIP)</li> <li>• American Medical Association (AMA)</li> <li>• National Association of Managed Care Physicians (NAMCP)</li> </ul>
Medical organization associations	<ul style="list-style-type: none"> <li>• National Comprehensive Cancer Network (NCCN)</li> <li>• Association of American Medical Colleges (AAMC)</li> </ul>
Disease-focused associations	<ul style="list-style-type: none"> <li>• American Diabetes Association (ADA)</li> <li>• American College of Medical Genetics (ACMG)</li> <li>• American Heart Association (AHA)</li> </ul>
Scientific and clinical professional associations	<ul style="list-style-type: none"> <li>• American Association of Clinical Chemistry (AACC)</li> <li>• American Association for the Advancement of Science (AAAS)</li> </ul>
Life sciences industry associations	<ul style="list-style-type: none"> <li>• Advanced Medical Technology Association (AdvaMed)</li> <li>• American Clinical Laboratory Association (ACLA)</li> <li>• Biotechnology Industry Organization (BIO)</li> <li>• Pharmaceutical Research and Manufacturers of America (PhRMA)</li> </ul>
Health care quality and efficiency organizations	<ul style="list-style-type: none"> <li>• American Health Information Management Association (AHIMA)</li> <li>• National Committee for Quality Assurance (NCQA)</li> <li>• National Quality Forum (NQF)</li> </ul>
Special interest consortia	<ul style="list-style-type: none"> <li>• Genetic Alliance</li> <li>• National Patient Advocate Foundation (NPAF)</li> <li>• Personalized Medicine Coalition (PMC)</li> </ul>

Category	Example Organizations
Health research professional organizations	<ul style="list-style-type: none"> <li>• Academy Health</li> <li>• Institute of Medicine (IOM)</li> <li>• International Society of Pharmacoeconomics and Outcomes Research (ISPOR)</li> <li>• Health Technology Assessment International (HTAi)</li> </ul>

While the majority of professional societies are nonprofit organizations, it is important to note that these organizations are service-oriented businesses. They certainly help to advance science and health practice, but also protect the interest of their members. As such, professional society success and viability depend on development of offerings valuable to member’s education, decision making, and business operations. Development of niche-oriented or unique areas of emphasis that are sustainable in relation to competing offerings of other professional offerings and other stakeholders (e.g., conference coordinating businesses, government and commercial agencies) is also common.

As with any other business, professional societies also have financial, staff, and other limitations that influence the scope and nature of the activities that they can feasibly engage in. In other words, no single professional society has the capacity to “be all things to all people” and play a role in all activities relevant to personalized health care. Despite the potential interest in or importance of any particular topic or effort, society activities must be identified and prioritized based on alignment with mission, key objectives, capabilities, and member needs.

Understanding the specific areas of focus of a relevant professional society is important to identifying the role that it may play in advancing health services or policy changes. Is the organization message-oriented (e.g., in the context of policy making), content-oriented (e.g., development of clinical practice guidelines and standards), or both? Key activities relevant to personalized health care that professional societies currently engage in include, but are not limited to the following activities. Many organizations will engage in more than one, but not all of these activities.

- 1. Clinician education, training, and certification:** Professional societies have historically played a fundamental role in offering services that support continuing medical education. Education and training can be delivered in a variety of forms including a peer-reviewed journal operated by the society, newsletters, Webinars, and white papers on key clinical topics. Professional conferences and workshops are also important venues for learning about the latest trends in technology, health services delivery and management, and their implications for future business practices.

Many societies also offer formal training and certification necessary to maintain current licensure for clinical professionals. Others, such as the American College

of Cardiology and American Society of Clinical Oncology develop and offer interactive educational portals and resources for physicians that cover a range of topics aimed at keeping practicing clinicians current on clinical, business, and policy issues important to their practice.

- 2. Clinician decision support and information management:** Within the current “age of information overload,” the efficiency of accessing and managing information key to clinical decision making is important to appropriate health care decision making. Although existing systems may range from broad information interfaces to very specific applications such as drug dosing (e.g., safe dosing the anticoagulant warfarin for prevention of thrombosis and embolism) or targeted therapy selection, most decision support systems are not generally maintained by professional societies.<sup>47</sup> Expansion of complex molecular diagnostics and need to improve treatment use and outcomes will escalate the need for such systems as adjuncts to standard clinical practice in the near future.<sup>48</sup> As these systems continue to develop, professional societies will contribute to ensure appropriate alignment and currency for clinical practice.<sup>49</sup>

As use of genetic and biomarker-based information is increasingly implemented in clinical practice, physician decision support systems that incorporate evidence-based practices and decision steps will need to expand or evolve to accommodate information on individuality.<sup>50</sup> It will also be important to understand how and to what extent health care processes and decision tools that emphasize standardization (e.g., clinical practice guidelines, clinical pathways, quality programs) should incorporate individual patient information to balance potential improved outcomes of individualized care with the costs of this approach.

- 3. Patient education and decision support:** Some professional societies emphasize patient education and informed clinical decision making. This mission includes providing basic education on disease pathology and outcomes, diagnosis, and treatment alternatives, implications for patient subpopulations, and other resources helpful to the patient. The American Diabetes Association (ADA), American Heart Association (AHA), American Cancer Society (ACS), and many others have highly diversified offerings targeted to the individual patient. Others, such as the National Patient Advocate Foundation (NPAF), collaborate with a variety of health stakeholders to ensure that the patient’s perspective is

<sup>47</sup> Bussey HI, Wittkowsky AK, Hylek EM, Walker MB. Genetic testing for warfarin dosing? not yet ready for prime time. *Pharmacotherapy* 2008;28(2):141-3.

<sup>48</sup> The value of diagnostics: innovation, adoption and diffusion into health care. Advanced Medical Technology Association. Jul 2005.

<sup>49</sup> Information technology for genetic and genomic based personalized medicine. The Harvard Medical School – Partners HealthCare Center for Genetics and Genomics 2008.  
<http://www.parliament.uk/documents/upload/stGMHarvardMedicalSchool.pdf>.

<sup>50</sup> Kawamoto K and Lobach DF. Clinical decision support for genomics and personalized medicine. Institute for Genome Sciences and Policy Medicine Forum. Duke University 2007.

appropriately included and represented in clinical practice change and health care reform initiatives.

Given the rapid expansion of available diagnostics and treatments, including those related to gene-based and personalized medicine, and the resulting maze of complex choices, patient-oriented information for informed decision making is important. Further, as cost shifting places greater responsibility for health services payment for on individual patients, evidence characterizing the benefits, risks, and value of health services is essential to informed decision making. While basic patient decision support systems have evolved, significant room is available for additional support from professional societies and other health stakeholders, particularly as interoperable health information technologies mature.

**4. Health outcomes research and new health technology evaluation:** One of the most important roles that professional societies play is in education, communication, and evaluation of new medical evidence supporting diagnosis, treatment, and health services delivery. This role includes not only vetting the findings of clinical studies, but also providing input on methodologies for study design, good clinical and laboratory practices, and evidence review. In general, such contributions include but are not limited to the following areas:

- (a) *Clinical study design and implementation support:* Most medical specialty societies do not contribute to clinical study design and implementation support to the same extent as life science manufacturers and government and academic researchers. However, professional society membership does enable members from various stakeholders groups to seek and obtain input from peers on these issues, including methods for incorporation of genes or biomarkers into clinical studies.

Other societies, such as the Institute for Pharmacogenomics and Outcomes Research (ISPOR) and Health Technology Assessment International (HTAi) emphasize development of good methodological practices for developing and evaluating evidence characterizing the value of new health technologies and practices. Organizations with a methodological focus may play a significant role in developing criteria, clinical and data modeling research approaches that help fill existing gaps in study approaches and evaluations for diagnostics, drug-diagnostics combinations, and database and registry evaluation that are relevant to personalized health care.

- (b) *Horizon scanning and HTA:* Evaluation of emerging health technologies is also an area where medical professional societies provide valuable input relevant to health practice. The conferences hosted by professional societies are one of the first places, prior to publication in peer-reviewed clinical and scientific journals, where ongoing and novel research findings are presented to clinical peers and other stakeholders for consideration. Such conferences are also where new health technologies may be introduced to the broader clinical community, and adoption, uptake, and diffusion considerations may be

discussed. This exposure to health interventions enables payers, policy makers, and other health stakeholders to scan the horizon for potential clinical, financial, and other impacts.<sup>51</sup>

While the process of clinical practice guideline development involves systematic assessment of evidence, many of these efforts are broad and do not focus on specific health technologies. Payers and external HTA bodies are most often the “first line” of health-related organizations to evaluate the clinical (and sometimes economic) value of individual new health technologies and considerations for appropriate use. However, the HTA process often involves clinical experts or key opinion leaders that are members of professional societies. Additionally, health technology evaluators may consult with medical specialty societies during the HTA process. Given the complexity of some emerging diagnostics and treatments (e.g., antibody-based biologics, cellular, and gene therapies), increased involvement of professional societies, manufacturers, and other stakeholders may be necessary to ensure informed technology adoption and use decisions.

- (c) *Clinical practice guidelines and practice standards*: Professional societies play a pivotal role in developing and maintaining clinical practice guidelines and informing practice standards or providing clinical pathways for evidence-based care provision. The National Guideline Clearinghouse, a comprehensive database of clinical practice guidelines maintained by the Agency for Healthcare Research and Quality (AHRQ), lists over 2,200 guidelines, the majority of which were developed and are updated by US and international medical specialty societies. Some of these guidelines are specific to a particular treatment indication and/or scenario. Other guidelines, such as those published by the American College of Rheumatology, National Comprehensive Cancer Network, and American Heart Association are comprehensive resources covering multiple indications or disease areas.

Development of clinical practice guidelines is often a significant and costly undertaking for professional societies. The process often involves systematic review and evaluation of the best available evidence, as well as multiple rounds of review and revision by members, appointed clinical advisory boards, and external stakeholders. Incorporating relevant and actionable information on individual variation into clinical guidelines will introduce greater complexity and decision steps versus current standardized methods of practice. Ultimately these guidelines may be adapted into health quality and performance programs.

At present, the circumstances where genomic and biomarker-based information should be included in clinical practice guidelines generally occurs in a nonstandardized case-by-case basis (as warranted) and is relatively

<sup>51</sup> Ibid.

limited compared to what may be the case in 5 to 7 years. While clinical practice guidelines focus on standardization, integration of individualized information in the most appropriate format to support broad applications in general practice is somewhat uncertain (e.g., inclusion in clinical practice guidelines, physician reminder programs, decision support systems).

- (d) *Database and data clearinghouse standards and support:* As new health data becomes more readily available and accessible, databases and patient data registries that contain extensive demographic, clinical, utilization, and other information will be a key foundation element of personalized health care. While professional societies do not currently play a significant direct role in developing and maintaining clinical databases (this is largely done by government, payers, and providers), current examples that have been informed by professional societies include claims databases, electronic health record databases, clinical trial data registries, and health quality or performance data sets. In general, databases specifically relevant to utilization of genetic and biomarker-based tests are limited in number and design.<sup>52</sup> These often longitudinal and information rich resources may also be used in clinical and health services research that will augment and in some ways transcend results of conventional clinical research.

Databases and registries can help link use of particular interventions to long-term effectiveness and safety outcomes, enable “real world” evaluation of health technologies, and provide population-level data necessary to appropriately refine health practices in the face of new knowledge. While a myriad of such databases already exist, at present most are not yet sufficiently interoperable to handle the complex applications anticipated for personalized health care. It is also important to note that these databases require strong organizational supports and funding to establish and maintain, as well as substantive input from clinical, statistical, HIT, and other experts to ensure appropriate functionality and usefulness. Such constraints are currently significant limiting factors.

As databases and registries increasingly include genetic and biomarker information and develop interoperability, issues such as scope and anticipated use, relevant expertise, and funding sources will influence the degree and rate of database development. In the absence of proper stakeholder incentives, fully interoperable databases and information systems may not mature for some time.

- 5. Health quality and pay-for-performance standards:** Development of health quality measures is another activity that some societies engage in. Health quality measures, like clinical practice guidelines, are evidence-based and focused on

<sup>52</sup> Infrastructure to monitor utilization and outcomes of gene-based applications. Agency for Healthcare Research and Quality 2008.

characterizing standards of clinical practice and patient care. As previously discussed, these measures are often used in provider and physician performance management programs, including P4P programs that tie financial incentives to performance.

While some societies such as the National Quality Forum (NQF), National Committee on Quality Assurance (NCQA), and the Leapfrog Group focus on health quality evaluation and measure development, medical specialty societies may also contribute by translating elements of evidence-based clinical practice guidelines into health quality measures useful in P4P approaches. The extent to which information on individual variation will be integrated into health quality measures is currently uncertain because these approaches leverage quality and efficiency gains based on standardizing health care delivery.

- 6. Educate and inform evolving health management practices and operational models:** Although most professional societies focus efforts on clinical aspects of medical education, many also provide education, training, resources, and certification related to business management of provider, payer, and other health-related organizations. For example, the National Association of Managed Care Physicians (NAMCP) conducts medical director training “academies” to teach the business skills that clinically-oriented physicians will need to succeed in provider and payer administrative roles. Where personalized health practices will affect processes (e.g., clinical pathways or guidelines, quality measurement and P4P programs) that have financial and operational implications for professional society members, future member training may include education on the implications of individualized health information on health management practices and provider operations.
- 7. Stakeholder collaboration, communication, and coordination:** Professional societies currently play an essential role in bringing together key health stakeholders (e.g., payers, providers, employers, manufacturers, policy makers) to advance debate and seek solutions regarding emerging health care issues. Professional societies often have much broader “reach” (versus individual stakeholders) into diverse stakeholder groups that can be utilized to address issues and challenges through workshops, advisory councils, and other initiatives. Some personalized health issues are likely to be sufficiently complex that they will warrant collaboration among professional societies (and other stakeholders) to appropriately address certain education, operational, or health policy issues.

Likewise, since professional societies represent a group of health professionals with similar interests, the collective “voice” of the society is often more influential than individual members or member organizations acting alone. Accordingly, societies may also develop opinion and policy statements, practice standards, decision tools, and business practice recommendations, which could include topics germane to personalized health care. The conferences hosted by professional societies provide virtually unparalleled opportunities for addressing



health care issues through open sessions, workshops, collaborative initiatives and even informal dialogue among stakeholders.

- 8. Rational health policy development that supports viable business models and care delivery practices focused on personalized health care:** The activities of professional societies include not only commercial stakeholders such as payers, providers, health technology manufacturers, and HIT companies, but also public stakeholders in government and policy (e.g., CMS, FDA, AHRQ, and CDC). Professional societies have historically worked on a variety of levels to directly and indirectly inform rational health policy development that supports quality clinical practice and innovation in health delivery. For example, life sciences industry organizations such as the Advanced Medical Technology Association (AdvaMed), the Biotechnology Industry Organization (BIO) and others regularly interact with a medical specialty societies and policy makers to inform thoughtful development of health policies that support appropriate health technology adoption and use on a range of topics particularly relevant to personalized health practice.

While not all professional societies are directly involved in the policy making process, most play a role in education and stimulation of healthy debate and discussion of key health services delivery and management issues. In the emerging era of integration of information on individual variation, broad engagement of professional societies will be critical to development and refinement of sound health policies that integrate personalized health care approaches into standardized and complex policy and delivery scenarios. As personalized health care approaches themselves become accepted as standard over time, professional societies will also be important contributors to implementation and harmonization efforts in the global health care environment.

Although professional societies currently play a role in many activities necessary for successful implementation of personalized health practices, emphasis and participation in particular activities will vary markedly by organization. Accordingly, level of interest and willingness to devote resources to personalized health care initiatives will depend upon the organization's mission, nature of offerings (e.g., content development, message development, policy processes), availability of funding, and relevancy to members. However, as personalized health practices evolve, it is clear that professional societies are poised to facilitate collaboration among key stakeholders and play a role in development of processes, standards, and business practices that incorporate information on individual variation.

### **Assumptions Regarding Future Dynamics of Health Care Delivery**

To understand the role that professional societies may play in supporting transition to personalized health practices, it is important to consider the implications of health care trends and the future dynamics of health care delivery. For purposes of discussion, we will assume a timeline of 3 to 5 years following the publication of this paper and evaluate the likely state of certain factors, listed below, important to broad implementation of personalized health practices and implications for professional societies.

## **Factor 1: Gene-based and Other Molecular Tests are Routinely Used in Patient Management**

While events such as sequencing the human genome have markedly advanced our scientific knowledge, the reality is that a tremendous amount of additional research will be necessary to understand how and in what ways information on individual variation can be used in routine clinical practice. The process of science and clinical discovery simply takes time, even given the rapid pace of technological innovation and emphasis on accelerating the translation of research into practice. Despite the promise of personalized health care, the convergence of science, medicine, and technology will not occur overnight.<sup>53</sup> In general, it takes up to 20 years to move a new treatment or intervention from research into clinical practice.<sup>54</sup>

At present, while use of diagnostic tests is routine in clinical practice, application of complex molecular diagnostics remains comparatively limited for a variety of reasons. These reasons include, but are not limited to physician and patient educational needs, uncertain reimbursement scenarios, and complexity of interpretation. However, as biomarkers are increasingly studied in clinical trials in the coming years, evidence linking diagnostic test information to treatment selection and health services delivery issues will expand in tandem. At present there are approximately 121 drug labels in the US that contain pharmacogenomic information, 69 of which refer to human genomic biomarkers, which is a fair beginning for personalized medicine following publication of a complete draft of the human genome in 2003.<sup>55</sup> Recent efforts, such as the partnership announced in October 2008 between the FDA and Medco (one of the largest pharmacy benefits management organizations), are poised to further accelerate associations between pharmacogenomics and treatment decision making.<sup>56</sup>

Another key challenge will be overcoming educational barriers for use of some complex tests in physician decision making, particularly in the context of general and family practice.<sup>57,58</sup> To fully integrate personalized health care, it will be important to create an environment where physician ordering and interpretation and patterns of test use linked to treatment selection/utilization are standard practice. It is likely that expanded emphasis on personalized medicine and information management will occur in clinical and health care management training programs in the next 3 to 5 years, and this is already occurring

<sup>53</sup> Faulkner E. The road to personalized health care: translating promise into practice. *J Manag Care Med* 2007;(10)6:25.

<sup>54</sup> Personalized Health Care. Opportunities, Pathways, Resources. United States Department of Health and Human Services. 2007. Accessed September 28, 2007: <http://www.hhs.gov/myhealthcare/news/phc-report.pdf>.

<sup>55</sup> Frueh F, Amur S, Mummaneni P, et al. Pharmacogenomic biomarker information in drug labels approved by the United States Food and Drug Administration: prevalence of related drug use. *Pharmacotherapy* 2008;28(8):992-998.

<sup>56</sup> Genomic updates to drug labeling could result from Medco/FDA partnership.

<sup>57</sup> Ghosh AK. Dealing with medical uncertainty: a physician's perspective. *Minn Med*. 2004;87(10):48-51.

<sup>58</sup> Ghosh AK and Ghosh K. Translating evidence-based information into effective risk communication: current challenges and opportunities. *J Lab Clin Med*. 2005;145(4):171-80.

in academic settings that train new health professionals. To expedite this educational process, professional societies can play a key role in creating and supporting medical education and certification programs, training on emerging decision support systems, and promoting a learning and collaborative environment for personalized health care.

**Factor 2: US HTA and Reimbursement Infrastructure Sufficiently Enables Personalized Health Care**

While 55% to 65% of US medical and pharmacy directors and physician decision makers feel that personalized medicine will be transformative and usher in new paradigms of personalized care delivery, a recent survey conducted by the National Association of Managed Care Physicians (NAMCP) indicates that these gatekeepers and decision makers recognize the following key challenges facing personalized health care.<sup>59</sup>

- Limited information linking diagnostic information to treatment decisions and outcomes
- Inconsistent definitions of clinical utility for diagnostics
- Limitations of current HTA practices (i.e., not sufficiently geared for personalized health scenarios)
- Physician and health practitioner understanding and adoption
- Limited uptake of electronic health records and information systems for implementing personalized health care approaches

Many of these issues relate to processes for evidence-based practice, HTA, and translation of research into clinical practice. At present, there is significant uncertainty regarding evidentiary requirements and decision criteria for diagnostics, drug-diagnostic combinations, costly biologics and other scenarios relevant to personalized health care, particularly from the perspective of third-party payers and policy makers.<sup>60,61</sup> Because of this uncertainty, public and commercial payers (e.g., CMS and the Blue Cross Blue Shield Association), government-affiliated groups (e.g., EGAPP), and private organizations (e.g., ECRI Institute, Hayes, Inc.) are beginning to develop approaches to overcome these obstacles, fill existing gaps, and provide information relevant to decision makers.<sup>62</sup> Professional societies can liaise with these stakeholders to ensure that clinical

<sup>59</sup> Based upon data from a 2007-08 comprehensive web-based survey of the membership of the National Association of Managed Care Physicians. Of the 150 total responses, 62 were from managed care organization (MCO) decision makers (predominately medical and pharmacy directors), 31 were from health system and hospital administrators and provider decision makers, 6 were from large US employers or purchaser organizations, and 10 represented commercial life sciences manufacturers. (publications in progress).

<sup>60</sup> Payer principles. Personalized Medicine Coalition. Accessed August 28, 2008:

[http://www.personalizedmedicinecoalition.org/sciencepolicy/payer\\_principles.php](http://www.personalizedmedicinecoalition.org/sciencepolicy/payer_principles.php).

<sup>61</sup> Faulkner E. Oncology biomarkers: reimbursement implications for diagnostics and therapeutics. Presented at the GTC Bio Oncology Biomarkers: From Discovery to Validation Conference, San Francisco, CA 2008.

<sup>62</sup> Appleby C. Making the case to managed care. *Biotechnology healthcare* Dec. 2004:16-25.

and methodological perspectives and implementation issues are appropriately aligned will “real world” decision making needs.

Recent authoritative reports produced by the Institute of Medicine; the Secretary’s Advisory Committee on Genetics, Health and Society; and AdvaMed have also cited significant insufficiencies in the reimbursement systems associated with molecular diagnostics. Insufficiencies include HTA and coverage processes associated with diagnostics, as well as medical coding and payment approaches that do not keep pace with technological development or do not appropriately reflect the value of tests to patient care and health outcomes.<sup>63,64,65</sup> As some of these barriers to innovation and expansion of personalized health practice are addressed over the coming 3 to 5 years, professional societies can play an important role in informing development of rational policies and health delivery practices.

**Factor 3: Prevention and Risk Assessment Approaches that Incorporate Genetic Testing are Standard Practice**

In large part, incentives in the US health care delivery system are geared to support “sickness care” and not “wellness care” that focuses on early disease identification and prevention. Because of the large volume and costs associated with preventive health efforts, including screening of asymptomatic patients at risk for disease development, the evidentiary threshold for demonstrating value is high and uptake has been historically limited. For example, Medicare statute prevents use of screening and prevention tests, except as amended by Congress. Since the late 1960s, fewer than 20 diagnostic tests have been approved for screening applications, including coverage of staple tests such as cholesterol testing, prostate-specific antigen testing, fecal occult blood testing and diabetic screening.<sup>66</sup> Additionally, as employment longevity has decreased in the US, commercial health plans have historically been reluctant to support preventive testing for beneficiaries that may only remain in the plan for 12 to 24 months in scenarios where disease may occur years later.

Greater emphasis from a variety of stakeholders and different incentive structures supporting preventive health services will be necessary to fully realize personalized health efforts in the coming years. Professional societies can play a variety of roles in supporting advancement of preventive health services, ranging from providing input on the viability and business implications of preventive health strategies and applicability of emerging technologies to influencing appropriate policies that support “wellness care.”

<sup>63</sup> Diffusion and Use of Genomic Innovations in Health and Medicine. Institute of Medicine 2008.

<sup>64</sup> Realizing the Potential of Pharmacogenomics: Opportunities and Challenges. Secretary’s Advisory Committee on Genetics Health and Society 2007.

<sup>65</sup> The value of diagnostics: innovation, adoption and diffusion into health care. Advanced Medical Technology Association. Jul 2005.

<sup>66</sup> A better Medicare for healthier seniors: recommendations to modernize Medicare's prevention policies. Washington, DC: Partnership for Prevention 2003.

Efforts may also include member education and training on how preventive and disease management programs can incorporate information on individual variation and maintain efficiencies gained by practice standardization.

**Factor 4:** Electronic Health Records and Decision Support Systems are a Mainstay in Hospital and Multi-physician Practices

As previously discussed, low provider adoption of electronic health records (EHR) and lack of interoperable health information systems will limit our ability to provide personalized health services. Further, the decision support tools that would improve processes for leveraging individual health information are presently in an early stage of development. Despite government, commercial MCOs, and other initiatives that provide incentives for providers to quickly adopt these systems, issues such as perceived benefit/burden tradeoffs associated with this capital investment, implementation concerns, the pace of technology turnover, and lack of standardized approaches will remain substantial barriers to acceptance over the next 3 to 5 years.

Factors that would be necessary to support EHRs and decision support systems adoption and implementation for personalized health practices include:

- Systems that help to identify treatment practices beneficial to specific patient subgroups. Development of systems with these capabilities will be strongly influenced by the use of EHRs and decision support systems within the overall market and demand based upon perceived benefits of customization.
- Knowledge translation practices based on differential patient outcomes.
- Standards for integrating this information into clinical practice guidelines and quality measurement and/or performance management programs at the multi-physician practice level and the individual level.
- Federal and other incentives for providers to collect and report data (in a standard format from EHRs) on gene-based and other molecular test information.

The government and private sector must provide strong incentives to support uptake of interoperable health information systems and their evolution as broadly adopted and routine tools to guide care practice. Sound policy and payment incentives that encourage well-developed provider organizations in addition to data reporting requirements that currently provide disincentives for nonparticipation will expedite HIT uptake and use.

As health information capabilities and knowledge networks evolve, professional societies may play a role in developing the content of clinical decision support systems and/or managing population-level data from member organizations if business incentives are appropriate to support these actions. Professional societies must consider either the availability of a suitable customer base willing to pay to access this information or the viability of partnering opportunities with HER vendors or physician practices/health systems.

**Factor 5: Provider Education and Certification is Increasingly Tied to Health Care Quality and Best Practices Initiatives**

Provider education delivered by both academic educational centers and professional societies has recently increased emphasis on topics such as use of biomarkers in medical decision making, disease prevention and management, implications of genomics and personalized medicine on managed care, and trends in electronic health records and quality/performance management programs. However, education offerings relevant to personalized health care are currently geared towards making the fundamentals of this topic comprehensible to providers, payers, and other health stakeholders. Further, medical certification and licensure requirements for many physicians do not yet include elements of personalized health care, but will likely need to in the future.

As clinical standards and quality measures emerge that incorporate elements of personalized health practice, professional societies can play a strong role in creation of tools that are appropriately aligned with health delivery practices and patient needs. Such tools, if supported by federally-funded initiatives and MCOs, are likely to initially target high cost/high need chronic disease areas (e.g., diabetes, heart disease, cancer).

However, the extent to which patient-specific guidelines and measures incorporating elements of individual variation will be implemented into quality management and health reform efforts is currently uncertain. At present, the majority of clinical guidelines often lack appropriate specificity for development of quality and performance measures, without adding individual variability into the mix.<sup>67,68</sup> In addition, the ability to which we can incorporate personalized health information into clinical decision support systems is still a nascent area with significant room for development.<sup>69</sup>

**Factor 6: Professional Societies Play a Key Role in Evidence Evaluation and Implementation of Knowledge into Clinical Practice**

Professional societies have historically played a key role in the translation of new knowledge and technology into clinical practice. It is reasonable to assume that in the future, this role will extend to personalized health practice. However, the pace of innovation and our capacity for generating information outstrips our capacity to translate new knowledge into meaningful health improvements. As such, professional societies will serve to help clinicians and other stakeholders adapt to technological innovation, information management, and new business practices that are the foundation elements of personalized health care.

<sup>67</sup> Renner P, Renner P, Didebahn R, Bullock AN Challenges in developing quality performance measures for geriatric populations. Abstr Acad Health Serv Res Health Policy Meet 2002;19:33.

<sup>68</sup> Quality matters: patient-centered care. The Commonwealth Fund 2007;Volume 23

<sup>69</sup> Schoenbaum SC. Can care be patient-centered and clinically efficient? Bulletin of the Royal College of Pathologists July 2007;139:27–30.

Education on the expanding range of new diagnostic and treatment technologies will be critical to correct use of personalized health care technologies. Professional societies can aid in the evaluation and introduction of new technologies and clinical practices by serving as an interface between various health stakeholders, including payers, providers, and technology developers. As previously discussed, this mediation will occur through activities such as providing input on methods and standards for health outcomes and comparative effectiveness research, development of clinical practice guidelines and health quality measures, and informing development of practical tools for knowledge management and clinical/business decision making.

As part of the process of knowledge transfer, professional and scientific societies may also play a role in the conceptualization and validation of viable business models for personalized health care. In part, this can be accomplished by hosting conferences, workshops, and focus groups that address issues relevant to personalized health care practice and policy. As business models emerge, society activities will also include training of physicians and other clinical care providers to ensure that health delivery processes and standards appropriately incorporate knowledge of genetics and individual variation.

### **A Framework for Professional Societies to Play a Role in Enabling Delivery of Personalized Health Care**

*What Framework is Needed to Address Personalized Health Care?:* In considering a framework that HHS might adopt to encourage uptake and implementation of personalized health care practices, it is important to recognize key barriers and then align strategic initiatives to overcome them. The validation, adoption, and diffusion of personalized health care practices may be limited by several barriers, many of which are common to introduction of any new health technologies and/or changes in clinical practice or standards of care (see Table 3).

In the case of personalized health care, failure to overcome any one of these barriers will influence not only the rate and range of stakeholder acceptance, but also holds the potential to forestall integration of some practice applications altogether. For example the level of uptake of health information management systems and business model implications are two factors that would broadly delay personalized health care efforts on the whole. Another key factor is that the concept of personalized health care is sufficiently comprehensive that unless it is broken down into actionable elements, it will be difficult to address and operationalize.

**Table 3: Key Barriers to Integrating Personalized Health Care Into US Health Care Offerings**

Action Category	Barrier
Break down integration of personalized health care into discrete tasks	<ul style="list-style-type: none"> <li>▪ Characterizing specific initiatives relevant to personalized health care in a manner where anticipated stakeholder involvement is well defined and focused on clear objectives</li> <li>▪ Leveraging stakeholders (including professional societies) that are instrumental in accomplishing a particular goal or initiative</li> </ul>
Develop appropriate evidence and information to meet decision needs	<ul style="list-style-type: none"> <li>▪ State of the science and ability to implement personalized health care practices in a clinically meaningful manner               <ul style="list-style-type: none"> <li>– Clinical trial, registry, and database standards</li> <li>– Pilot and demonstration programs</li> <li>– Disease-specific focus areas</li> </ul> </li> <li>▪ HTA and evidence-based practice methodological limitations (including acceptance of novel clinical trial and data modeling approaches)               <ul style="list-style-type: none"> <li>– Diagnostics (including molecular diagnostics)</li> <li>– Treatments subject to personalized medicine scenarios</li> <li>– Combination product scenarios (involving diagnostics, drugs and devices)</li> <li>– Innovative methods focusing on “least burdensome” approaches that provide “need to know” evidence</li> </ul> </li> <li>▪ Communication of medical and personalized health information in a cost-shifting and information overload environment               <ul style="list-style-type: none"> <li>– Address the information needs of providers, payers, and patients</li> </ul> </li> <li>▪ Inefficient processes for translating clinical research into practice (including clinical guidelines and practice standards, quality measures and performance management programs)               <ul style="list-style-type: none"> <li>– Clinical guidelines and practice standards</li> <li>– Health care quality measures</li> <li>– Approaches for vetting decision tools and processes relevant to provider</li> </ul> </li> </ul>
Define business plans and	<ul style="list-style-type: none"> <li>▪ HTA and evidence-based practice implementation limitations (i.e., standardized processes do not</li> </ul>



Action Category	Barrier
appropriate operational policies	<p>anticipate personalized health care approaches)</p> <ul style="list-style-type: none"> <li>▪ State of interoperable EHRs and decision support systems and their level of uptake in practice <ul style="list-style-type: none"> <li>– Health information technology and decision support system adoption issues</li> <li>– Data collection and reporting standards and policies</li> <li>– Data analysis approaches</li> </ul> </li> <li>▪ Business model, operational, and policy implications of integrating personalized approaches into processes that seek to gain efficiencies through standardization</li> </ul>
Implement plans for personalized health care	<ul style="list-style-type: none"> <li>▪ Bringing stakeholders together to collaborate on appropriate policies and implementation plans</li> <li>▪ Insufficient incentives for health care stakeholder participation <ul style="list-style-type: none"> <li>– Manufacturer</li> <li>– Hospital and clinician</li> <li>– Health plan</li> <li>– Professional society</li> <li>– Patient</li> </ul> </li> <li>▪ Implementation costs of personalized health care approaches, including lack of transparent and/or viable public/private partnership models</li> <li>▪ Approach for pulling the various discrete tasks together and monitoring implication and impact of personalized health care <ul style="list-style-type: none"> <li>– Collaboration and stakeholder engagement</li> <li>– Oversight and cross-functional alignment</li> </ul> </li> <li>▪ Approach for influencing changes to improve quality and efficiency of operational elements (as appropriate)</li> </ul>

These action categories (including associated barriers), form a very general framework from which HHS and key health stakeholders can parcel out and address elements critical to implementing personalized health care. While not specific to personalized health care, it should be noted that a variety of US government initiatives geared towards addressing these barriers are already in motion.

For example, the National Institutes of Health (NIH) and the AHRQ have implemented a variety of initiatives aimed at addressing translation of research into practice over the past

decade.<sup>70,71</sup> The Centers for Disease Control and Prevention (CDC) and FDA have also made strides in recent years regarding integration on information on patient variability into technology evaluation and population-health programs. Likewise, in 2004 President George W. Bush outlined a plan to support adoption of interoperable EHRs and issued an Executive Order to create a National Coordinator for Health Information Technology within the Office of the Secretary of HHS to facilitate this plan.<sup>72</sup> These are just a few examples of existing HHS efforts that can be leveraged to explore opportunities for improving personalized health practice.

Understanding how to weave personalized health care into this framework in a manner that is not duplicative of existing efforts is also an important consideration for HHS, but outside of the scope of this white paper. Factors such as strong leadership support, data to support implementation start-up and evaluation, degree of required organizational change, collaboration requirements, sustainability planning, and dissemination infrastructure have played significant roles in the overall rate of adoption and diffusion and would also be relevant to making progress against a framework for personalized health care.<sup>73</sup> By clearly defining objectives and anticipated outcomes, the approaches and relevant stakeholders necessary to advance personalized health care will be more transparent and easier to accomplish and will enable appropriate prioritization among objectives.

*Integrating Professional Societies Into a Framework that Supports Personalized Health Care:* As strategies for operationalizing personalized health care practices continue to move forward, professional societies will play a pivotal role, both in regard to short-term evaluation and planning, as well as long-term implementation support. Such organizations are unique in their ability to connect key health stakeholders, provide a neutral grounds for healthy debate and discussion, enable educational and health practice tools and solutions, and support “big picture” objectives outside of the capacity of individual member or affiliate organizations.

In regard to engaging professional societies in efforts targeting personalized health care practices, many societies may embrace the promise of personalized health care, but remain uncertain about specific action steps and their implications for members. Because professional societies operate as any other business, the greater the clarity of a proposed engagement, the easier the evaluation of relevance and participation becomes.

<sup>70</sup> Re-engineering the clinical research enterprise: translational research. NIH Roadmap for Medical Research. National Institutes of Health 2008. [www.nih.gov](http://www.nih.gov).

<sup>71</sup> Translating research into practice II: fact sheet. Agency for Healthcare Research and Quality 2001. <http://www.ahrq.gov/research/trip2fac.htm>.

<sup>72</sup> Promoting innovation and competitiveness: President Bush’s technology agenda. 2004. [http://www.whitehouse.gov/infocus/technology/economic\\_policy200404/chap3.html](http://www.whitehouse.gov/infocus/technology/economic_policy200404/chap3.html).

<sup>73</sup> Bradley EH, Webster TR, Baker D, et al. Translating research into practice: speeding the adoption of innovative health care programs. *Commonwealth Fund* 2004;(724):1-12.

As HHS supports key practice and policy efforts in this area, the following business and operational requirements will be key to anticipating the scope and nature of relevant professional society participation:

- Alignment with society mission and vision
  - Perceived relevance to member interests and needs
  - Perceived relevance to funding organizations that enable key products or offerings
  - Alignment with specific “deliverable” offerings and tradeoffs necessary for implementation
  - Implications for competition with other professional societies or stakeholders
  - Benefits and risks of stakeholder partnerships around key goals and objectives
  - Funding requirements (for implementation and sustainability)
- Similar to the manner in which barriers to personalized medicine may limit adoption and uptake, it will be important for HHS and other stakeholders in the vanguard of personalized health care to anticipate the extent to which specific initiatives will appeal to professional societies. The more closely aligned the desired objective is with these requirements, the greater the likelihood of securing participation.

### **The Road Ahead: Enabling the Personalized Health Care Environment**

Personalized health care is a complex concept involving many aspects of health quality and efficiency improvement. Because the concept is broad and far reaching, it will be challenging to predict and plan for all of the health delivery and systemic implications of increasing integration of individual variability in health practice. While initial steps will likely be addressed on a scenario-by-scenario basis, it will be important to maintain perspective on the implications for health care delivery on the whole as personalized health care unfolds.

Information inputs envisioned for personalized health care appear to be potentially boundless and complex. In an age of information overload, it will be essential to channel knowledge into decision support systems, “smart tools,” and delivery approaches that better inform health decisions and presumably generate better health outcomes.<sup>74</sup> If integrated effectively, these changes in health care delivery may also refocus our current “sickness-based” system on disease prediction and prevention. The most effective models will balance standardization, best practices, and population gains with personalized health care practices, with greater emphasis placed on one or the other as appropriate to the scenario.

<sup>74</sup> Faulkner E. The road to personalized health care: translating promise into practice. *J Manag Care Med* 2007;(10)6:25.

It is clear that professional societies have a fundamental role to play in the new era of personalized health care. While some issues and operational processes will lend themselves to personalization more readily than others, professional societies are cognizant of the potential benefits of personalized health care in a US health environment facing serious challenges and hard decisions. Appropriate engagement of professional societies around specific and well-defined personalized health care issues will require complex orchestration and planning on the part of HHS. Nevertheless, weaving professional societies into decision and implementation steps is likely to confer far reaching benefits by mobilizing key stakeholders and establishing a rational and balanced pathway forward.

Successful implementation of personalized health care will rely on the ability of key health stakeholders to work collaboratively towards practical and sustainable health solutions. Policy makers, professional organizations, payers, providers, employers, health technology manufacturers, and patients must all develop a common understanding of the cause and effect of decisions regarding integration of personalized health practices, including implications for particular stakeholders or market segments. In light of escalating health care costs and threats to sustainable provision of health services, the opportunities represented by personalized health care are great, as is the price of failure to collaboratively forge well founded solutions for the road ahead.

Stakeholder Type	Drivers/Incentives	Implications for Personalized Health Care
Medical Professional Societies	<ul style="list-style-type: none"> <li>▪ Improve care and health delivery practices</li> <li>▪ Focus on organizational mission and vision</li> <li>▪ Provide education and support to members</li> <li>▪ Maintain operational status by developing offerings/services that provide value to members</li> </ul>	<ul style="list-style-type: none"> <li>▪ Implications of personalized health care for medical professional societies will depend upon the organization's mission, nature of offerings (e.g., content development, message development, policy), and relevancy to members.</li> <li>▪ Medical professional societies can serve as a bridge between stakeholders by providing opportunities for engagement such as annual conferences, working sessions, position and policy statements, Webinars, and other outreach activities.</li> </ul>
Provider Organizations	<ul style="list-style-type: none"> <li>▪ Improve patient health outcomes</li> <li>▪ Serve patients and the community</li> <li>▪ Offer current and appropriate health services</li> <li>▪ Maintain profitable and competitive service offerings</li> <li>▪ Meet quality and P4P milestones (if applicable)</li> </ul>	<ul style="list-style-type: none"> <li>▪ While personalized health care information offers opportunities for improved treatment selection, patient management, and health outcomes, need for education and decision support for physicians remains critical. Personalized health information must be collected and communicated in a format that is readily useful to the physician during a typical patient consultation.</li> <li>▪ As information on genetic and other variability becomes increasingly available (e.g., via guidelines, standards of practice) the need for concise, easy-to-use decision support tools will become more pronounced.</li> <li>▪ Personalized health data will also add to administrative data collection and reporting requirements in addition to those associated with claims processing, quality, P4P, health transparency, and other initiatives.</li> </ul>

Stakeholder Type	Drivers/Incentives	Implications for Personalized Health Care
		<ul style="list-style-type: none"> <li>▪ Provider adoption of electronic health records will limit the uptake and diffusion of systems and practices that promote personalized health care.</li> </ul>
Health Insurance Plans	<ul style="list-style-type: none"> <li>▪ Administer health plan assets effectively via policy creation, contracting, and processing of claims <ul style="list-style-type: none"> <li>– Ensure the quality and affordability of beneficiary services</li> <li>– Ensure beneficiary access to the broadest array of beneficial services</li> <li>– Limit access to unproven/unnecessary services and/or health technologies</li> </ul> </li> <li>▪ Maintain profitable and competitive service offerings</li> </ul>	<ul style="list-style-type: none"> <li>▪ Health insurance plans will likely embrace aspects of personalized health care that better characterize value of new health technologies for particular patient categories. This knowledge will be implemented through coverage policies, claims review, quality and P4P initiatives and other programs.</li> <li>▪ On the one hand, payer leveraging of personalized health information will support patient access to the right treatment at the right time and dose where evidence of benefit is clear, presumably improving quality and effectiveness. On the other hand, overly aggressive approaches by payers have the potential to prematurely limit patient access to beneficial technologies based on incomplete information on population versus subpopulation safety and effectiveness.</li> <li>▪ Compared to treatments, criteria and processes for evaluating emerging diagnostics is not clear or well defined from the payer perspective. While such processes are likely to emerge in the next 1 to 2 years, uncertainty regarding clinical utility is likely to result in coverage limitations/noncoverage for tests without a clear value proposition.</li> <li>▪ Evidence assessment for diagnostics and treatments</li> </ul>

Stakeholder Type	Drivers/Incentives	Implications for Personalized Health Care
		<p>may be conducted by different groups within a payer organization. Noncoverage of a test that is directly linked to treatment use (e.g., as recommended in the product label) may limit or preclude patient access to the treatment in some scenarios.</p> <ul style="list-style-type: none"> <li>▪ Increased uptake in electronic health records and availability of longitudinal databases that contain personalized health information may ultimately enable identification of “real world” trends in treatment response not captured in manufacturer pivotal or postmarketing studies and more refined population-level beneficiary management capabilities.</li> </ul>
Diagnostics Manufacturers	<ul style="list-style-type: none"> <li>▪ Develop innovative health technologies that improve patient care/health outcomes in areas of unmet need</li> <li>▪ Create and maintain market opportunities for pipeline health technologies <ul style="list-style-type: none"> <li>– At the highest volume and price supported by the market</li> <li>– That withstand pressures of competition, changing health policies and service delivery trends</li> </ul> </li> <li>▪ Increase revenue and meet expectations of external investors/stockholders</li> </ul>	<ul style="list-style-type: none"> <li>▪ Because diagnostics do not have similarly robust profit margins compared to drugs, opportunities for innovation must be balanced carefully against the following factors. Improvement in one or more of these limitations to diagnostic adoption and diffusion would increase manufacturer incentives to develop additional tests and decision support offerings. <ul style="list-style-type: none"> <li>– Increasing evidentiary (e.g., direct evidence of clinical utility) and funding requirements—for more complex and costly studies than have historically been required for demonstrating the value of diagnostics</li> <li>– Outdated and uncertain coding and payment structures that do not fully characterize or value tests (which represent 2% to 3% of US health</li> </ul> </li> </ul>

Stakeholder Type	Drivers/Incentives	Implications for Personalized Health Care
		<p>care expenditures but influence over 75% of health decisions)</p> <ul style="list-style-type: none"> <li>– Limited stakeholder support of preventive/predictive applications, particularly screening of asymptomatic patients</li> <li>▪ Additionally, because diagnostics may be developed through either the FDA or Clinical Laboratory Improvement Ammendments (CLIA) mechanisms, nonmanufacturer health stakeholders have questioned the differential evidence on product safety, effectiveness and value resulting from these mechanisms. More consistent evidence requirements would improve stakeholder assessment of diagnostics as new test development increases significantly over the coming years.</li> </ul>
Treatment Manufacturers	<ul style="list-style-type: none"> <li>▪ Develop innovative health technologies that improve patient care/health outcomes in areas of unmet need</li> <li>▪ Create and maintain market opportunities for pipeline health technologies <ul style="list-style-type: none"> <li>– At the highest volume and price supported by the market</li> <li>– That withstand pressures of competition, changing health policies and service delivery trends</li> <li>– Increase revenue and meet</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▪ Drug and biologics manufacturers: While treatment manufacturers initially resisted drug development approaches that would limit treatments to patient subpopulations in favor of the blockbuster approaches, health reform trends, increasing reimbursement hurdles, and the success of forerunner personalized medicine approaches appear to be changing this perspective. <ul style="list-style-type: none"> <li>– Emphasis on personalized health practice remains limited, but is expanding.</li> <li>– Obtaining coverage for a limited market is preferable to non-coverage as payers</li> </ul> </li> </ul>



Stakeholder Type	Drivers/Incentives	Implications for Personalized Health Care
	<p>expectations of external investors/stockholders</p>	<p>increasingly limit coverage based upon differential evidence of value.</p> <ul style="list-style-type: none"> <li>– The most widely embraced use of genomic and related information is to “salvage” treatments that may fail to be approved for broader use but where benefits to specific patient subgroups are transparent.</li> <li>– Proactive approaches (e.g., drug-diagnostic codevelopment) are expanding as manufacturers realize the potential for securing limited markets at viable price points.</li> <li>– Increasing propensity for regulator label changes based on the growing knowledge base correlating biomarkers and treatment response requires manufacturers to alter perspectives on personalized health care.</li> </ul>
<p>Policy Makers and Regulatory Agencies</p>	<ul style="list-style-type: none"> <li>▪ Ensure that health services are sufficiently safe and effective</li> <li>▪ Ensure that access to health services are provided in an ethical and efficient manner</li> <li>▪ Improve access to beneficial health technologies and services by supporting R&amp;D and translation of research into clinical practice</li> </ul>	<ul style="list-style-type: none"> <li>▪ Emphasis on personalized health care must be balanced against other competing efforts that seek to improve the quality and effectiveness of health care in the US. However, personalized health care is broadly related to many ongoing health reform efforts and consideration of the implications of integrating information based upon genetic variability would be relevant to many ongoing HHS and public/private partnership efforts.</li> </ul>
<p>Patients</p>	<ul style="list-style-type: none"> <li>▪ Access the broadest selection of quality health services</li> </ul>	<ul style="list-style-type: none"> <li>▪ Increased patient cost sharing is a key consideration for personalized health care. Going forward, patient</li> </ul>

Stakeholder Type	Drivers/Incentives	Implications for Personalized Health Care
	<ul style="list-style-type: none"> <li>▪ Ensure that health services are affordable in the context of other financial and life requirements</li> <li>▪ Maintain the lowest possible hurdles or obstacles to access</li> </ul>	<p>choices will be influenced by a variety of factors, including perception of need, disease severity, payer and provider barriers to care access, financial tradeoffs required to medical care and availability of alternatives.</p> <ul style="list-style-type: none"> <li>▪ Patient selection of and access to personalized/targeted health services that may be priced higher than existing alternatives, will be determined by health plan design (e.g., copay structures, use of health savings accounts) and affordability of these care options.</li> </ul>

**Sources:** The value of diagnostics: innovation, adoption and diffusion into health care. Advanced Medical Technology Association. Jul 2005; Overcoming barriers to electronic health record adoption. Health Care Financial Management Association 2006; Knowing what works in health care: a roadmap for the nation. Institute of Medicine. National Academy of Sciences 2008; and Faulkner E. The road to personalized health care: translating promise into practice. J Manag Care Med 2007;(10)6:25.

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# The Role of the Academic Medical Center in Advancing Personalized Health Care

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The use of genomic, molecular, and imaging technologies holds the promise of improved medical decision-making and advancement towards personalized healthcare<sup>1</sup>. Yet, despite the vast number of research discoveries based on the genome sciences, relatively few have been translated into medical practice. The pharmaceutical industry has developed only a handful of ‘targeted therapies’ such as trastuzumab, imatinib, and erlotinib that use molecular diagnostic tests to identify patients who are likely to benefit. Diagnostic companies offer a similarly sparse repertoire of new genomics-based molecular diagnostics that can be readily deployed in the course of care. Of the few genetic tests that have been approved by the FDA many are based on genetic variation that has been known for decades<sup>2</sup>. In short, the market has been challenged to move personalized health care from a ‘nice concept’ to a reality in clinical practice.

Each of the stakeholders in healthcare delivery stands to gain from a more comprehensive strategy to implement personalized medicine in health care systems (See Table 1). For example, payors will realize savings from lower use of ineffective drugs, patients will avoid adverse drug reactions, and diagnostic companies will realize higher margins on their tests. Despite these obvious advantages, investment in the clinical development and deployment of personalized medicine discoveries has been modest at best. The comparatively low development activity of the personalized medicine discoveries may be attributed to the fact that, aside from a few exceptional cases, the value created by commercializing personalized medicine cannot efficiently reach those required to invest in its development.

The goal of making genomics clinically relevant and realizing the full potential of personalized healthcare (PHC) can be achieved if market forces and regulatory policies are aligned, such that academia, industry, government, payors, and advocacy groups are

motivated to share information and resources while equitably distributing the resulting increase economic value. Academic Medical Centers (AMCs), as the locus of discovery, validation, and clinical implementation of these new tools, will be a key enabler of this strategy. Specialized centers or institutes within AMCs focused on personalized medicine will serve to foster collaboration, information sharing, and appropriate handoffs among the diverse group of stakeholders. These centers will facilitate the development of consensus evidentiary standards for new technologies to be adopted into clinical practice and define common data standards to prospectively collect and share knowledge of the complex association of biology, health and disease progression. It will be incumbent upon AMCs to play a leadership role in enabling the realization of PHC by developing and implementing new organizational, care delivery, and funding models as well as adopting new intellectual property licensing and conflict of interest policies<sup>3</sup>.

**Players across Healthcare Value Chain Stand to Benefit from Increasing Prevalence of Personalized Medicine**

<b>Pharma Cos.</b>	<ul style="list-style-type: none"> <li>• Enhance clinical trials (faster, smaller, higher POS)</li> <li>• Diversify Rx through higher efficacy, tolerability and/or safety</li> </ul>
<b>Diagnostic Cos.</b>	<ul style="list-style-type: none"> <li>• Introduce specialized tests with higher margins</li> <li>• Spearhead drug development initiatives</li> </ul>
<b>Regulators</b>	<ul style="list-style-type: none"> <li>• Improve certainty of drug efficacy and avoid side effects</li> <li>• Faster approvals</li> </ul>
<b>Providers</b>	<ul style="list-style-type: none"> <li>• Deliver differentiated and better care to patients</li> <li>• Derive value from patient data</li> </ul>
<b>Payors</b>	<ul style="list-style-type: none"> <li>• Reduce high cost of ADRs and ineffective drugs</li> <li>• Earlier diagnosis impacts costs, but not always positive</li> </ul>
<b>Patients</b>	<ul style="list-style-type: none"> <li>• Improved drug safety and efficacy</li> <li>• Personal knowledge of their risks and value of therapy</li> </ul>
<b>Physician</b>	<ul style="list-style-type: none"> <li>• Potential to deliver better care to patients</li> <li>• New sources of revenue from KOL consulting</li> </ul>

Source: McKinsey & Company

The translation of genome based discoveries, novel biomarkers, and predictive models from bench to bedside are fundamental to the development of PHC. A four-phase framework (T1, T2, T3, and T4) has been proposed by Khoury, et al., to describe this “translational continuum” (Table 1)<sup>4</sup>. A successful PHC application will need to traverse discovery to initial (“first in human”) health application (T1), clinical validation to evidence-based guidelines (T2), to general clinical practice (T3), and to population and public health impact (T4). The AMC will play a role in each phase and must partner and/or adapt its organization and policies to advance new health care models in order to achieve the full impact of these innovations.

**Table 1**

<b>The continuum of translation research in genomic and personalized medicine: types of research</b>		
<b>Translation research phase</b>	<b>Notation</b>	<b>Types of research</b>
<b>T1</b>	<b>Discovery to candidate health application</b>	<b>Phases I and II clinical trials; observational studies</b>
<b>T2</b>	<b>Health application to evidence-based practice guidelines</b>	<b>Phase II clinical trials; observational studies; evidence synthesis and guidelines development</b>
<b>T3</b>	<b>Practice guidelines to health practice</b>	<b>Dissemination research; implementation research; diffusion research Phase IV clinical trials</b>
<b>T4</b>	<b>Practice to population health impact</b>	<b>Outcomes research (included many disciplines); population monitoring of morbidity, mortality, benefits and risk</b>

### **AMCs as sources discovery in personalized medicine (T1)**

AMCs are uniquely suited to discover and perform the preliminary development of the next generation of biomarkers. On AMC campuses the physical juxtaposition of academic research, medical education, leading technologies, and clinical care provides an excellent environment for investigators to develop an understanding of the unmet needs of the market, to discover novel solutions, and to validate their efficacy in experimental models and in clinical cohorts and test their utility in ‘real world’ healthcare delivery settings.

Academic researchers, unlike researchers in private industry whose budgets are primarily dictated by expected investment returns, have the freedom to explore new areas of science with less immediate regard to financial return on investment. Moreover, academic research aspires to operate with norms of Mertonian “open science” as opposed to the generally more proprietary model of R&D in industry. Consequently, AMCs can more readily collaborate, build off one another’s discoveries, and foster more “disruptive thinking” that can bring about new technologies and approaches and introduce entirely new capabilities, rather than incremental refinement and improvement on existing techniques.

**AMCs: a strong record of innovation.** Academic research institutions have contributed many of the discoveries leading to genomic technologies. The basic methods of DNA synthesis were pioneered at the University of Colorado by Marvin Carruthers. The Maxam-Gilbert DNA sequencing method was developed primarily at Harvard, and Sanger-Coulson sequencing at the University of Cambridge. The prototype for automated Sanger sequencing, using the four-color fluorescent method, was pioneered at Caltech. DNA-chip microarray technologies commercialized by Affymetrix and Agilent drew on Stanford research, and the Illumina bead-array technology grew out of analytical chemistry at Tufts University. Some of these methods were patented (four-color DNA sequencing, DNA lithography, bead-arrays); some were not (Sanger-Coulson and Maxam-Gilbert sequencing). Sequencing methods were widely adopted for academic research, but large-scale sequencing depended on instruments developed by Applied Biosystems and other firms, and microarray technologies were developed by many

companies. Competition for the new generation of high-throughput DNA sequencing, en route to the \$1,000 genome, is intense among several firms and academic researchers.

Academic research centers have also been deeply involved in another set of discoveries directly pertinent to the advance of genomics-guided medicine – the association of an individual’s molecular biology, both static (e.g., DNA sequence, gene copy numbers, and single nucleotide polymorphisms SNPs) and dynamic (e.g., gene expression, protein and metabolite levels), with clinical phenotypes. Genomics-guided medicine has grown out of the quest for disease-associated genes that accelerated in the 1980s. This revolution began when genetic linkage maps were used to find mutations associated with Mendelian conditions such as Huntington’s disease and cystic fibrosis. It then expanded into Mendelian forms of diseases with multiple causes, such as Alzheimer’s disease, and inherited susceptibility to conditions such as breast and ovarian cancer or colon cancer. Genetic testing, once restricted to a handful of newborn screening tests, has expanded to include hundreds of tests. At the end of August 2008, for example, [www.genetests.org](http://www.genetests.org) listed 595 laboratories testing for 1610 conditions.<sup>5</sup> With the commercialization of efficient discovery platforms for the measurement of dynamic biological parameters such as gene transcription factors, proteins and metabolites in the 1990’s, genomics-guided medicine expanded to include diagnosis and prognosis of non-Mendelian conditions. Hundreds of gene expression, protein, and metabolite “signatures” are under investigation at AMC’s and diagnostic companies as potential tools for use in PHC. Arguably, these T1 research efforts are only possible because of the ability of academic investigators to ascertain and bank high quality clinical specimens from patients and to link these to robust clinical phenotypic data and longitudinal follow up and health outcomes (see below).

Cancer research today is a spectacularly promising example of the AMC’s role in shaping the future of genomics-based personalized cancer care. “The Cancer Genome Atlas,” collaboration between the National Cancer Institute and the National Human Genome Research Institute and several AMC’s, aims to develop novel tools for the detection and treatment of cancer. This program utilizes technologies such as large-scale genome sequencing (of germ line and somatic DNA) to better understand the molecular basis of a variety of tumors (glioma, non-small cell lung cancers, and ovarian cancer). The overarching goal of this project is to improve capabilities for preventing, diagnosing, and treating cancer at a personalized level. This program and others will result in a paradigm of medical care based on our ability to match accurate prognosis and proper therapy to the molecular characteristics of the individual and with the individual patient’s tumor. Whole-genome expression data from this effort and other in the AMC’s are now being used routinely to identify subtypes of cancer not previously recognized by traditional methods of analysis: profiles and patterns that identify new subclasses of tumors, such as the distinction between acute myeloid leukemia and acute lymphoblastic leukemia<sup>6</sup>, or Burkitt’s lymphoma from diffuse B cell lymphomas<sup>7</sup>, without prior knowledge of the classes. More recently several genomic signatures that go beyond disease classification have been discovered and validated that predict prognosis and response to therapy for many solid tumors and hematologic malignancies.<sup>8,9</sup> Much of the science that underlies associating genomic data with clinical decisions has and will continue to come from AMC’s. For now, these technologies are mainly research tools, but they will surely become relevant to clinical decisions with the proper investment in their development.

**Funding of innovation: A changing landscape.** AMCs have been the main recipients of grants for health research, and home to most “public domain” research from which further research and practical applications arise. Innovative technologies described above have resulted in part from these funding streams. A survey estimated government and nonprofit genomics research and development (R&D) spending from 2004-2006 at \$3 billion annually,<sup>10</sup> in rough parity to a separate survey that estimated private genomics R&D at \$3 billion.<sup>11,12</sup> This balance between private and public genomics R&D is a dramatic change from the early 1990s, when private genomics funding was sparse. By 2000, however, the \$2 billion R&D expenditures by publicly traded firms wholly or partially devoted to genomics and another \$1 billion genomics R&D at established pharmaceutical and biotechnology firms exceeded the \$1.8 billion reported in government and nonprofit R&D.<sup>13</sup> Private genomics R&D is a major force now; AMCs are at the point of convergence between government and nonprofit funded genomics R&D and privately funded genomics, although we know of no estimate of private genomics R&D at AMCs. How these funding shifts will affect the balance between innovation in the AMCs and private firms is uncertain; public-private partnerships (see “A Call for Specialized Centers” below) may yield the greatest productivity from these investments, and AMCs will be essential elements of such partnerships.

**Role of Intellectual Property in developing personalized medicine at AMCs.**

Academic institutions own a much larger share of patents relevant to DNA diagnostics and prognostics than in most other areas of technology, because much of the research studying linkages between genomic factors and disease is federally funded through the NIH or other government and nonprofit sources—with a disproportionately large fraction conducted at research institutions associated with medical schools.<sup>14</sup> While AMCs account for somewhat less than 2 percent of patents overall,<sup>15</sup> government funded research institutions accounted for 39 percent of DNA-based patents 1980-1993,<sup>16</sup> a more than ten-fold enrichment of academic patent ownership compared to patents overall. A preliminary analysis of patents licensed by one major diagnostics firm, Athena Diagnostics, showed more than three-quarters of the relevant “gene” patents were owned by academic institutions.<sup>17</sup>

This prominent role of academic research institutions suggests that sometimes AMCs will be patent owners, sometimes they will need to license patents owned by others, often they will be working in conditions of uncertainty about whether their research—and even more so, commercialization strategies—enjoy freedom to operate or will be subject to patent enforcement. This is starkly different from the patent regime long associated with protein and small-molecule therapeutics, where the zone of uncertainty is smaller because only one or a few key patents cover a small class of molecules. However for business plans being developed today, complex patent landscapes portend uncertainty for the future of DNA-based technologies.

The practice of AMCs governing patenting and licensing of genomic technologies, as both users of the inventions and also as patent-owners, is crucial. Academic institutions have emerged as owners of intellectual property for several reasons. The main reason is that the research they do is fully intended to have practical benefits, creating knowledge that enables development of products and services to improve health. Most health



research falls squarely in what the late Donald Stokes called, “Pasteur’s Quadrant,” meaning it is both scientifically important and also has foreseeable practical use.<sup>18</sup> It thus often produces results that can be patented because they are novel, useful, and inventive.

Universities, in the past, have patented some inventions, including drugs and vaccines. Thyroid hormone, vitamin D, warfarin, insulin, and antibiotics (although notably not penicillin) were first described in patents owned and administered by academic institutions. However, the level of academic patenting accelerated in the 1980s, mainly because of the science and technology being pursued, but also because the Bayh-Dole Act of 1980 clarified the default rules for ownership of patents.<sup>19</sup> The Bayh-Dole Act increased consistency among federal R&D funding agencies and it codified the emerging practice of having grantee and contractor institutions own patent rights, rather than government retaining ownership of patents arising in federally funded research. Thus the Bayh-Dole created an incentive for academic institutions to seek patents so they could license them.

Academic institutions responded accordingly by getting many more patents, and this effect, as noted above, is particularly pronounced in DNA-based technologies. Commercial biotechnology in general, and genomics in particular, grew up almost entirely in the Bayh-Dole era, with incentives for universities and AMCs to patent inventions arising from research, and giving them control of licensing of the resulting intellectual property. The development of the Affymetrix chip technology, for example, drew upon Stanford research and personnel, entailed several grants directly to the nascent company, and benefited from federally funded research.<sup>20</sup> The development of Illumina technology is also a classic Bayh-Dole story of a research idea at Tufts being developed by a startup firm with exclusive rights to university patents.<sup>21</sup> In both cases, a big part of the first market for the resulting technology was academic health research, so universities were involved in creating the technologies and later benefited from the availability of powerful new instruments developed by startup firms.

Many DNA patents have been exclusively licensed, and many of the uses of those patents were not foreseen at the time the patents issued and licenses were signed. For DNA sequence patents exclusively licensed for the full patent duration of the patent, even if the exclusive rights were restricted to diagnostic use, these prior intellectual property rights could cast a shadow over the development of genome-wide diagnostics, or over the first-generation “personal genomics” services that have recently become possible through companies like Navigenics, 23andMe, deCODEme, SeqWright, and Knome. The degree to which a legacy of existing patents and licenses affects the future of multi-gene tests will depend on: (1) the specific language of patent claims, (2) specific terms under which the patents have been licensed, (3) the outcome of any cases that set precedents in litigation, and (4) decisions about whether and to what degree patent rights are enforced against the new uses.

As DNA patent holders and also users of the technologies, AMCs will be making these choices. It will be a challenge. Patents and their claims are public, but collecting and analyzing all the relevant patents and interpreting how their claims might affect for a multi-gene test is a daunting task fraught with uncertainty. It is made even more difficult because terms of licenses, which are crucial to determining the boundaries of intellectual

property, are generally not public unless licensors and licensees choose to make them so. To the degree AMCs contribute to this inefficiency, they may impede the advance of genomic discoveries into medicine.

**AMCs role in biobanking and patient registries: important sources of discovery and validation for novel molecular tools for PHC.** As medicine moves toward PHC, molecular analyses of biological samples will provide a critical component of clinical decision-making. Well-annotated biospecimen collections have enabled the recent identification of genes and genetic loci with over 180 publications documenting over 660 SNPs that appear to contribute to susceptibility and survival to over 100 complex diseases<sup>22,23,24,25</sup> ([www.genome.gov/26525384](http://www.genome.gov/26525384)). Indeed, the acceleration of the clinical application of genomic testing and public health planning (T1 through T4) will be greatly influenced by how quickly AMCs can develop and adopt standards and protocols for sample acquisition, storage, and annotation and their integration into the mainstream of patient care. More than 300 million human biospecimens were stored in freezers across AMCs in the United States in 2000, with an estimated 20 million additional specimens being accrued yearly<sup>26</sup>. The NCI estimated that it spends greater than \$50 million yearly on banking samples from cancer patients as part of 125 funded research programs and projects.<sup>27,15</sup> The pharmaceutical industry is shifting to a clinical trial paradigm requiring that subjects provide samples with the hope of creating a new model for successful clinical development based on biomarkers derived from the analysis of these samples.

Despite this increased recognition of the role of human biospecimens as a critical enabler of genomics-based research and medical care, the state of storage of human biospecimens is largely in disarray.<sup>28</sup> Most AMCs cannot readily access a list of samples stored on institutional premises, the conditions under which they are stored or the subjects who donated them. The current lack of standards and quality control procedures for sample procurement to biological analyses presents a significant challenge to developing studies of statistical and clinical value as well as to guide public health planning and raises issues concerning the appropriate use of these samples donated by human subjects. Working with the NIH, AMCs have made progress in standardizing practice to facilitate knowledge sharing across institutions. In 2004, the NCI initiated the Cancer Bioinformatics Information Grid (caBIG) to standardize data formats for genomic and phenotypic data captured in cancer research and to develop common research tools among more than 50 NCI-designated cancer centers. Specific biomedical research tools under development by caBIG include clinical trial management systems, tissue banks and pathology tools, imaging tools, and a rich collection of integrative cancer research applications.<sup>29</sup>

Centralized biorepositories and standardized patient registries are aligned with the mission of AMCs and health systems to enable and enhance research opportunities as well as to assist in the structure to support health care delivery. Centralization will manage costs, create synergies and economies of scale, reduce liability, maintain high ethical standards, and enable compliance with applicable regulations. Research and funding opportunities will undoubtedly be enhanced through a centralized system that provides timely access to a large numbers of fully annotated samples, thereby minimizing the need to enroll new subjects and collect new specimens for each study. In addition, centralized biorepositories make costs more transparent and allow the AMC-investigator

community to carry out its research and clinical mission more efficiently, rather than spend its time managing sample collections. Longitudinal cohort studies rich in epidemiologic data combined with biospecimen banking create unparalleled scientific power. As we discuss below, biospecimen banks are not only a valuable source for discovery, but in cases where data has been collected over long periods of time, biobanks may allow for the efficient validation of biomarkers for their association with distant clinical endpoints that would be prohibitively expensive to validate prospectively.

Well-annotated biospecimens collections can also be leveraged successfully into academic-industry partnerships whose goal is improved diagnostics and therapeutics development. Merck & Co and Tampa's H. Lee Moffitt Cancer Center & Research Institute have formed a for-profit center, M2GEN, to collect tissues and clinical information of up to 30,000 consented research subjects with the aim of identifying biological differences that might explain variation in response to cancer drugs. The deal, valued at nearly \$100M over five years, gives Merck exclusive access to the database for drug discovery purposes. In a second collaboration, this time with a for-profit company medical device company, Merck partnered with Fox Hollow Technologies, Inc. of Redwood, CA. The partnership provided Merck access to Fox Hollow's collection of atherosclerotic plaques to test cardiovascular biomarkers for use as diagnostics and as tools for drug development. Similarly, BG Medicine – part of the High Risk Plaque (HRP) initiative, an industry consortium – is working with Duke University to identify biomarkers that identify patients at high risk for acute coronary syndromes using blood samples previously collected and stored by Duke's cardiac catheterization laboratory. The samples are linked to health outcomes data longitudinally through patient care within the Duke University Health System. These examples underscore the fact that research into PHC, both in academia and industry, could be greatly enhanced by more ready access to annotated patient samples to validate and develop new biomarkers.

Biobanks at research consortia funded by the NCI have played a central role in the development of Genomic Health's Oncotype Dx testing service to predict the risk of recurrence in early stage breast cancer patients. The initial list of candidate genes came from a search of the academic literature, mainly contributed by AMCs. Genomic Health refined its gene list and subsequently conducted two major validating clinical studies of the test entirely on tissues banked by the National Surgical Adjuvant Breast and Bowel Program (NSABP), a cooperative group based at the University of Pittsburgh. The two major cohorts used (B-14 and B-21) were collected in the 1980s. Without access to such tumor banks with "mature" clinical data, the T2 research necessary for clinical adoption would not have been possible in a timely or cost effective manner and investment and subsequent "translation" of the discovery would likely never have occurred. However, by carefully designed studies within the NSABP biobank cohorts, Genomic Health has been able to successfully launch Oncotype Dx and achieve reimbursement from most payers. Based in part on the data from these studies, the American Society of Clinical Oncologists (ASCO) has included Oncotype Dx in its most recent guidelines for the diagnosis and treatment of early stage breast cancer.

## **Resourcing the clinical validation of the next generation of personalized medicine (T2)**

Demonstrating the clinical utility of most the newly discovered genomic or imaging biomarkers through appropriately powered, randomized clinical trials has proven difficult for academic researchers and industry alike. When asked why genomic discoveries are not advanced to practice, stakeholders in PHC cite the lack of both public and private funding for clinical studies to build an evidence base and the challenges of designing and executing studies in which the clinical endpoints are separated from the interventions by many years<sup>30</sup>. Without clear evidentiary standards, investors cannot be certain of the level of funding necessary to achieve regulatory approval and payor acceptance of a new biomarker. In the face of this uncertainty, clinical validation is often left unfunded by the private sector. Indeed, there is a dearth of studies addressing the impact of new personalized medicine tools. In a survey of PubMed articles published between 2001 and 2006 on genomics and genetics in humans, only 2% of 336,169 manuscripts were classified as clinical trials. Of these trials, few were randomized.<sup>4</sup> Recognizing the need to develop studies that demonstrate the clinical value of genomics to inform clinical decision making and provide value, the Centers for Disease Control (CDC) and the NIH announced at least three RFAs this year to foster these types of studies.<sup>31</sup> The private sector has not been an enthusiastic funder of T2 research in personalized medicine. This is in stark contrast to clinical evidence produced each year funded by private industry to support the introduction of new therapeutics regulated by the FDA under the Pre-Market Approval (PMA) process for drugs, biologics, and devices. However, recently diagnostic development companies and the pharmaceutical industry have begun to, under certain scenarios, invest in personalized medicine and the T2 research studies necessary to drive their clinical adoption and prove their clinical utility.

**The Government as sponsor of T2 research.** CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group has begun the process of culling from the literature the genetic and genomic tests that have promise to shift the way health care is delivered. The first EGAPP report on the use of pharmacogenetic testing for prescribing tricyclic antidepressants was released in December 2007.<sup>32</sup> One of the areas EGAPP has identified for study is the use of gene expression profiles for prognosis in breast cancer – an area with a clear demand for a novel diagnostic solution. Of the women that receive adjuvant chemotherapy for node negative, estrogen receptor positive breast cancer, approximately 85% receive no clinical benefit over taking tamoxifen alone<sup>33</sup>. Despite the lack of a prospective randomized clinical trial – the gold standard for proving the value of an experimental therapy – oncologists used RNA expression signatures for risk stratification and prognosis in breast cancer for more than 24,000 “treat” vs. “no-treat” decisions in 2007<sup>34</sup>. A prospective cooperative group clinical trial (MINDACT) by the European Organization for Research and Treatment of Cancer aims to measure the effectiveness of a gene expression predictor of breast cancer prognosis to guiding adjuvant chemotherapy when compared to predictions based solely on the traditional clinical parameters for prognoses<sup>35</sup>. An NCI-sponsored study (TailorX) aims to utilize the Oncotype Dx test to identify low risk breast cancer patients unlikely to benefit from chemotherapy. A similar opportunity now exists to refine prognosis and redirect treatment in early stage lung cancer<sup>36</sup> and a CALGB sponsored clinical trial has been developed to use an expression signature to randomize patients to surgical treatment with or without adjuvant chemotherapy<sup>37</sup>. These are clear examples of

T2 research in which AMCs in collaboration with government and industry are developing novel clinical trials infrastructures to evaluate the performance of genomic medicine tools to redefine disease phenotypes and refine therapeutic strategies.

**Diagnostic companies as sponsors of T2 research.** In previous decades, private diagnostic companies have been reluctant to sponsor or conduct extensive clinical trials to demonstrate the clinical utility of novel assays, genomic or otherwise. This reluctance to invest has been driven primarily by economics. Under the current payor system a diagnostics company is reimbursed fixed fees for any procedures necessary to perform a test. Typically, these fees do not provide sufficient excess margin to justify an investment in extensive clinical validation, let alone patient and physician education or clinical guidelines development. Moreover, reimbursement by insurance companies has not generally been contingent on proving clinical utility in formal trials. Instead, tests had to be deemed “non-investigational”. As a result, most diagnostics on the market today have arrived after floundering in “investigational use” status as evidence and awareness slowly build up over time. Typically, a diagnostic company will develop a commercial version of a new test only once the biomarker has been sufficiently validated and gained acceptance within the clinical community. As exemplified by troponin testing for cardiovascular injury in the setting of chest pain<sup>38</sup>, the AMC has traditionally filled this validation role, often performing investigator-initiated trials and conducting the testing using their own, low-volume laboratory developed test (LDT), prior to the availability of a commercial test. This reluctance to invest in the validation of new diagnostics is often amplified when the performance characteristics of the technologies are less established – as is the case with many of the new genomic and multi-analyte platforms – and when the pathway to regulatory approval and ultimate clinical acceptance is less clear.

There is evidence, however, of a new model emerging for the investment in the development of novel personalized health diagnostics. The tests that receive such investment are often linked to expensive therapeutics and so can carry a high economic value. Under this new paradigm, a few private diagnostic companies, including Genomic Health, XDX, and Third Wave Technologies, have made the decision to invest in clinical trials conducted at AMCs, as well as the physician education and clinical guidelines development necessary to bring a novel test into widespread clinical use. This new model requires IP protection for the test, a clear path to a large market, and justification for a value-based price, which circumvents the traditional code-based reimbursement scheme. Only under these conditions can a private company be assured of an appropriate return on their investment.

A recent example of this new approach is the development of the Oncotype Dx testing service to predict the risk of recurrence in early stage breast cancer patients. Genomic Health invested over \$100 million in the clinical development and marketing of the test. However, with a price point of \$3,460 and an operating margin of over 60%, Genomic Health has a good chance of recouping its investment in the coming years. Genomic Health can justify its relatively high price for Oncotype Dx based on the potential value it brings to patients and their payers. By identifying those patients unlikely to experience a recurrence of their cancer and therefore unlikely to receive any benefit from adjuvant

chemotherapy, the test can in theory reduce the amount of money spent on chemotherapy and the management of its complications.

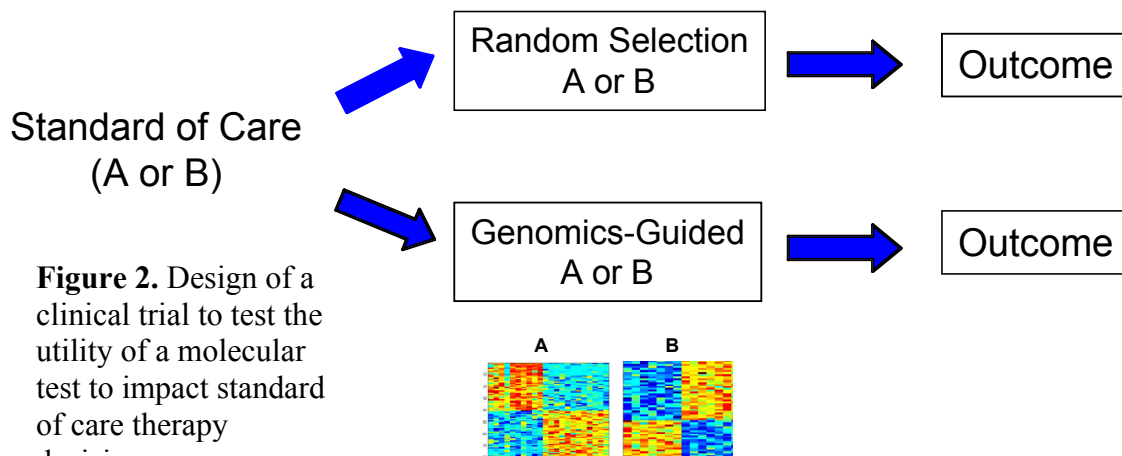
Genomic Health was able to identify an application in which the potential to save healthcare resources was high compared with the cost to demonstrate the clinical utility of the test and engage the patient and physician communities. Also, by securing patent protection for their test, they have been able to limit direct competition. However, very few new personalized health applications will have such attractive economics. Many other genomic discoveries have the potential to have a positive impact on healthcare delivery, but lack a clear path to near-term commercial profitability. The uncertainty surrounding what will be required for clinical validation and to secure approval by regulators and payors, and the lack of clarity in existing patent law to ensure exclusivity in the market discourage investment in all but clear economic winners. Until significant policy changes are implemented to reduce the uncertainty in validation requirements, level of and time to reimbursement, and ability to practice both freely and exclusively with regard to intellectual property, private investment will likely be limited.

**Pharmaceutical companies as sponsors of T2 research.** The pharmaceutical industry has the potential to be a significant driver of personalized medicine using genomic information to inform drug development, approval, and clinical drug use. At the same time, pharmaceutical firms have long resisted stratification strategies in clinical development and the resulting ‘segmentation’ of markets. For the most part, pharmaceutical developers are utilizing genomic approaches to identify which populations benefit from drugs after they are approved. Drug manufacturers would be wise to undertake such studies prior to approval. The lessons of cetuximab and EGFR mutations - driven by AMC investigator initiated studies to better understand the populations most likely to benefit from these agents - and recent late-stage drug failures have sounded an alarm. Indeed the FDA’s Critical Path Initiative challenges industry to adopt the use of biomarkers throughout drug development<sup>39</sup>. Voluntary Genomic Data Submissions to the FDA that began in 2005 encourage sponsors to incorporate genomics into their development plans<sup>40</sup> heralding that this may be a requirement in the future. The recent addition of genetic testing to the FDA label for warfarin<sup>41</sup> and the recent FDA approval of a microarray based test for the management of breast cancer<sup>42</sup> as well as a test for tumor of unknown primary<sup>43</sup> are clear signals that the regulatory environment will increasingly encourage medical product development based on genomic information. According to a recent survey by McKinsey and Co., biomarker R&D expenditures within

pharmaceutical firms in 2009 were estimated at \$5.3 billion, up from \$2.2 billion in 2003. This increase is targeted at the development of safety and pharmacokinetic biomarkers, and in so-called “companion diagnostics” – biomarkers that can accurately identify individuals with a high likelihood of response. Since most drugs show activity in only a fraction of patients, an industry-based strategy to use genomics to identify subgroups of patients most likely to benefit from their products in development will bring more personalized therapies to the market and will incorporate genomic testing into the labeling of the drugs ultimately approved.

### AMC-initiated T2 research studies

AMC investigators are now designing studies to test the hypothesis that genomics can improve outcomes for existing and standard of care therapies. At the Duke Institute of Genome Sciences & Policy this has been adopted as a strategy for translating genomics into clinical medicine. The IGSP Clinical Genomics Studies Unit (CGSU) has been established with the goal of setting the standard for genome-based clinical trials ([www.genomestohealth.org](http://www.genomestohealth.org)). This unit functions to vet the scientific merit of trials prospectively testing predictive genomic tests, assess technical and practical feasibility, and developing outcomes data to support clinical utility and cost effectiveness. A typical trial design that tests the ability of genetic or genomic information to improve clinical and economic outcomes underway in the CGSU is shown in figure 2 below.



**Figure 2.** Design of a clinical trial to test the utility of a molecular test to impact standard of care therapy decisions.

### Conflict of Interest in T2 research at AMCs

AMCs often face the vexing issues of conflict of interest that come with their role as neutral arbiters of the evidence surrounding use of medical technologies, both their benefits and their risks. “Opinion leaders” who influence the introduction and adoption of drugs, vaccines, biologics, and devices are typically drawn from prestigious AMCs. Congress is clearly concerned that the flow of money and other incentives for collaboration between academe and industry can also bias the research system in favor of corporate interests. The trade associations for the pharmaceutical, biotechnology and device industries have agreed to a succession of voluntary codes of conduct.<sup>44</sup> The Association of American Medical Colleges has issued several reports that make recommendations for managing both individual and institution conflicts of interest.<sup>45</sup> As the world’s largest single medical research laboratory, the NIH, tightened restrictions on

its federal employee researchers in 2002.<sup>46</sup> NIH also reminded its grantees and contractors of the need to have conflict-of-interest policies and its right to audit implementation of such policies in August 2008.<sup>47</sup> The government is also engaged in formal rule-making that could alter the rules. Several states have passed laws limiting gifts to physicians or mandating reporting of gifts over a certain amount (usually \$25 or \$50); Senators Grassley and Kohl have proposed a federal law mandating reporting of gifts and payments. Conflict of interest was a feature of the national magazine for state legislatures in September 2008.<sup>48</sup> Pennsylvania has funded a counter-detailing initiative to guide use of drugs, and many states have considered bills about direct-to-consumer advertising of medical products. Most of these proposed policy changes are primarily directed at drugs, but the policies are likely to spill over to change the overall system for introducing and adopting all new medical products and services, including genomic technologies.

#### **AMCs as platforms to study implementation of PHC delivery (T3) and outcomes (T4)**

The development and validation of clinical delivery models that support PHC is critical to its implementation and adoption. AMCs, for their part, have an opportunity to fundamentally change their approach to physician education, payment and incentive systems, and metrics of quality and efficiency and act as the first-line testing grounds for innovative T3 research. Moreover, by providing a platform with resident expertise in both clinical research and care delivery, AMCs have the opportunity to provide a common platform to all of the stakeholders for the conduct of the implantation, dissemination and health outcomes research necessary to see PHC brought into practice.

Although clinical care is a core mission of AMCs, as Snyderman and Yoedionio have suggested, academic medicine has not yet become engaged in the systematic exploration of more rational models for health care delivery required for personalized and prospective medicine.<sup>3</sup> Only a handful of AMCs have developed comprehensive programs enabling prospective approaches to patient care. In 2003, for instance, Duke University initiated Duke Prospective Health (DPH), a personalized care, disease management, and wellness program for its employees. The program, which Duke University physicians helped develop and manage, sought to prevent or detect chronic conditions related to smoking, diet, exercise, and stress by having patients develop and use a Personal Health Plan to ameliorate their individual risk. The program has three main components: a Health Risk Assessment (HRA), Care Management, and Health Coaching:

1. The HRA is a tool that analyzes lifestyle and habits and helps patients and their providers identify current and potential health issues necessitating attention. Patients use the results of their HRA to develop long-term strategic goals focused on health and wellness.
2. Care Management is where a care manager serves as the patient's point of contact and works with the patient to help formulate a Personal Health Plan that meets his or her health needs.



3. Health Coaching allows patients to work with a coach in a group setting who assists in facilitating the patients to achieve the goals of their Personal Health Plan.

Although the program is relatively new, preliminary analysis on 154 patients suggest that a multi-modality intervention reduced risk of CHD, by increasing exercise and improving weight loss.<sup>49</sup> Duke is now initiating comprehensive PHC programs that use the DPH as a core delivery model in breast cancer, prostate cancer, diabetes, cardiovascular medicine, pharmacogenomics, and family history.

### **Developing new economic models**

The premise of PHC is that by addressing health concerns pre-symptomatically – while interventions are more impactful and cost effective – health systems can improve health and lower the costs of health care. However, under the current economic models, any cost savings may not be realized by the health care providers bold enough to institute these changes. Currently, most payor systems do not reimburse for preventive services, except when Congress explicitly mandates it. Instead, reimbursement in the modern American health care system is driven by procedures and post-symptomatic interventions. Moreover, intensive in-patient procedures typically yield higher margins to the health systems than out-patient health monitoring and non-surgical interventions. PHC models, if successful, would shift patients from high-margin in-patient procedures to low-margin (or, at present, uncovered) out-patient screening and interventions. From the perspective of the healthcare systems' finance department, PHC is a money-losing proposition. With such misaligned incentives, personalized medicine approaches may not receive as enthusiastic backing as if it were equally profitable as current procedures, and therefore incentives to innovate in this area of health care delivery are lacking.

Similar countervailing financial incentives combined with an overall lack of compelling clinical data on new personalized health tools make it difficult for payors to fully embrace PHC. It may seem financially prudent for a payor to reimburse for a diagnostic test that could identify high-risk individuals in situations where relatively low-cost interventions could prevent expensive surgical procedures in the future. However, identifying those tools can be difficult. We have already examined the relative lack of clinical data on such tools on which payers might be able to make that determination. This uncertainty is compounded by the fact that even if a molecular diagnostic is shown to work, there is no guarantee that healthcare providers and/or their patient will modify their behavior in response to the result – in which case the payer may end up paying for the test and the surgical intervention. Finally, there is the “hazard” of discontinuity of coverage; due to the fact that people shift health coverage plans over their lifetime, a payor that covers a diagnostic screening for an individual will not necessarily receive the benefits of a healthier client in the coming decades. In fact there is an incentive for people to “game the system” by enrolling in relatively expensive plans which cover PHC, then once testing is complete, shift to a relatively less expensive plan for their long-term care. There are a few examples of situations where PHC has been covered by insurance. For example, Aetna and Kaiser will cover genetic counseling services under many of

their plans. Aetna has even instituted a phone counseling service for its members.<sup>50</sup> This may be financially motivated or for reasons of increasing service levels in a competitive health insurance market.

While all parties ultimately stand to gain from the implementation of PHC, economic incentives present significant barriers to realizing its implementation. It is incumbent upon AMCs to demonstrate leadership in the clinical delivery space by exploring new economic models, and serving as a common forum in which all stakeholders might share data and resources to overcome these barriers and work towards a scenario in which all parties benefit.

### **Quality, Performance, and PHC**

Personalized medicine will continue to meet resistance from individual practitioners unwilling to modify their patient management approach. Clinicians may resist if they feel that their judgment is being superseded by a test result or if they feel the way they have managed patients in the past was adequate. Without the proper systematic incentives in place, adherence to clinical guidelines and adoption of new therapeutics is often lackluster. For example, despite the publication of clinical evidence demonstrating the clinical utility of the use of beta-blockers for patients who were recovering from a myocardial infarction (MI) in 1981, in 1996 – 15 years after the landmark publications—these drugs were only prescribed to 62.5% of patients after an MI<sup>51</sup>. However, once physicians were evaluated based on their adherence to clinical practice guidelines, adoption increased rapidly. The National Committee for Quality Assurance (NCQA) began tracking compliance with certain treatment guidelines, including the use of beta-blockers in MI patients, in 1996 and publically reporting results. By 2006, compliance of beta-blocker administration had improved to over 97%.<sup>56</sup> The tendency to resist a change in practice holds true for all clinical care models, but will be especially true in the case of PHC. Adoption of new genomics-based tools will require health care providers to become familiar with new technologies and science and require continuing education on awareness on new PHC methods. AMC must make systemic changes in how health care providers are evaluated, compensated and trained if PHC is to be readily implemented and tie the concepts of PHC to quality, safety, and performance.

### **Health Professional and Public Education**

A core mission of the AMC is to train the healthcare workforce. As PHC services and diagnostic tools evolve, AMCs will need to develop training for the workforce that will be required to implement them. In our opinion, this is fundamental to bridging the third translational gap, T3, in the translational continuum. In this regard there is need to break new ground in medical education and to develop a national model for integrating knowledge of new molecular-based technologies in medical practice. The primary care workforce feels woefully unprepared to integrate genomics into regular practice<sup>52</sup>. Consumers are enthusiastic about genetics and are hopeful about their impact but at the

same time they have a low knowledge base about genetics and genetic testing for common diseases. Education of health professionals and the public must be a priority to advance the use of genomics into healthcare. With the rapid advances in genomics research and developing technologies, it will be challenging to keep health professionals informed about the benefits, risks, and limitations of new tools as they become available. In addition, the public and health care workforce will need to understand the appropriate clinical applications of genomic tools -- including their benefits, risks and limitations, and how they may improve clinical management. Direct to consumer genomic testing has only served to greatly intensify the educational needs across the genomic medicine community from the lay public to health care providers to policy makers. Several surveys have documented the below average physician knowledge of genetics<sup>53</sup>, but none has assessed knowledge of the newer field of genomics. The importance of education in the application of pharmacogenetics has been described<sup>54</sup>, but at present there are no broad initiatives to orchestrate genetics and genomics education of medical professionals, trainees, and the public at large. Basic genomic literacy is a critical need for patients and physicians and communities to engage in genomic research and clinical studies required bring about a change in the care paradigms to support clinical genomics applications.

In 2003, Duke University School of Medicine it revamped its curriculum and set as a goal to “practice personalized health planning for long-range goals”. Although this has not yet happened on a school wide scale, fourth-year electives such as Integrative Medicine and Prospective Health and Health Promotion and Disease Prevention are available. The fundamental concepts underlying the theory and practice of PHC should become central parts of medical education.<sup>3</sup> For the basic sciences, this would include teaching concepts of disease evolution from health and the role of predictive biomarkers in this process. Clinical education would include concepts of a medical evaluation comprising health risk prediction, current health status, pathogenesis tracking, pharmacogenetics, health planning, patient motivation, and disease management. To our knowledge, this has not yet occurred to any significant degree among U.S. medical schools or residency training programs. A strategy driven by the AMC community is essential to effect changes in the way the health care providers in medical and nursing students in the USA are trained in PHC.

### **Patient Centered Medical Home (PCMH)**

An important and emerging concept that will facilitate the implementation of PHC is the PCMH or the American College of Physician’s “Advanced Medical Home”. Enabling both T3 and T4 research, the PCMH is a model for delivery of care that is provided by medical practices to strengthen the physician-patient relationship by focusing on delivering coordinated care in a prospective manner – similar to the Duke Prospective Healthcare model above - to patients, focusing more on prevention of disease and promotion of wellness, compared to the current system of focus on episodic care based on illnesses and patient complaints. Genomic medicine should be integrated into each of the principles of the PCMH (Table 2): Personal physician, Physician directed medical

practice, Whole person orientation, Coordination/Integration of Medical Care, Quality and safety, and Access.

The PCMH is an opportunity to improve clinical operations and outcomes for patients in a currently fragmented medical system. The concept of genomic and personalized medicine has synergy with the PCMH in the effort to better define risk of chronic disease for individual patients, and to redefine how health risk is communicated to patients. Ongoing strategies for delivery of genomic or imaging based risk assessment technologies that enable PHC should focus on integration with the PCMH.

Table 2. The Advanced or Patient Centered Medical Home

Principles	Description
Personal Physician	<ul style="list-style-type: none"> <li>ongoing relationship with a personal physician</li> <li>trained to provide first contact, continuous and comprehensive care</li> <li>physicians must first be trained to understand the principles of genomic medicine</li> <li>provides a platform for implementation of strategies to improve the education of practicing physicians, residents and medical students in the applications of biomarkers, genomics, and predictive models to the practice of medicine.</li> </ul>
Physician Directed Medical Practice	<ul style="list-style-type: none"> <li>the personal physician leads a team</li> <li>team collectively take responsibility for the ongoing care of patients</li> <li>For genomic-based personalized medicine, this team needs to be defined</li> <li>possibly include clinical pharmacists, genomic and risk counselors, or genetic nurses as well as health coaches.</li> </ul>
Whole Person Orientation	<ul style="list-style-type: none"> <li>personal physician is responsible for providing for all the patient's health care needs</li> <li>responsibility for appropriately arranging care with other qualified professionals</li> <li>opportunities to introduce risk assessment to health through genomic medicine</li> </ul>
Care is Coordinated/Integrated	<ul style="list-style-type: none"> <li>care is coordinated and/or integrated across all elements of the complex health care system</li> <li>best facilitated by HIT and clinical decision support (CDS)</li> <li>for PHC, it will be critical for all participants in a patient's care to understand their family history, genetic background related to drug prescribing, and predicted risk for chronic conditions.</li> </ul>
Quality and Safety	<ul style="list-style-type: none"> <li>quality and safety are hallmarks of PCMH are also a natural endpoint of a PHC strategy</li> <li>evidence based medicine and CDS tools guide decision making, practices accept accountability for continuous quality improvement (CQI) through engagement in performance measurement and improvement</li> <li>patients actively participate in decision making and feedback is sought by the practice, IT is used appropriately to optimize care and data management</li> <li>appropriate recognition programs are followed to demonstrate that practices have the capability to provide patient centered services consistent with the PCMH model</li> </ul>
Access	<ul style="list-style-type: none"> <li>enhanced access to care and information</li> <li>medical homes and patients can securely post the genetic and molecular test results online</li> <li>interact via the internet to review test results</li> <li>communicate findings, and answer questions</li> <li>iteratively evolve a personalized health plan online.</li> </ul>

**Health information technology (HIT) and electronic health records (EHRs).**

Information technology will be a key component of both health care delivery and the T3 and T4 research that is needed for PHC. Past experience indicates that the new genomic interventions, like any new medical intervention, will remain significantly underutilized for some time without the concurrent introduction of supportive technologies. Moreover, genomic interventions may face even greater barriers to clinical adoption compared to more traditional medical interventions, due to such factors as patient concerns over genetic discrimination, limited clinician familiarity with the science, and the volume and complexity of the data that need to be considered. In recognizing this challenge, Secretary Leavitt announced in March 2007 HIT as a priority to support the achievement of personalized medicine.

The use of electronic medical records (EMRs) as a major component of HIT is expected to substantially improve the quality and efficiency of health care and provide an important vehicle to advance patient-centered personalized care. The use of EMRs in care delivery is expanding rapidly, especially among large integrated health delivery systems. The amount of clinically relevant molecular data and the number of resources devoted to research on genomic medicine are increasing in parallel. While the U.S. health system is fragmented, the large health systems that are adopting EMRs are becoming increasingly integrated, especially in adopting and implementing practice standards. Thus, a significant opportunity exists to incorporate various aspects of genetics, genomics, and predictive tools into the development of these emerging systems to facilitate adoption and clinical decision making.

An integral component of PHC is the application of family history to clinical care. Interest in collecting family history data as a routine part of care delivery is growing, as knowledge advances in linking family history of disease to patient risk. The need for the development of better family history tools has been highlighted by projects at the Centers for Disease Control (CDC) and by the U.S. Surgeon General's Family History Initiative<sup>55</sup>. However, these efforts have not directly addressed the integration of tools into the real-world scenario of busy physicians and a multiplicity of health record systems, and do not provide an adequate breadth of data capture necessary for research. The need for new tools is apparent; however, no such electronic family history tools have yet been developed, despite the availability of suitable technologies.

An important component of HHS's vision for the role of HIT in PHC is the use of computer systems to provide clinical decision support (CDS), defined as the act of providing clinicians, patients and other health care stakeholders with pertinent knowledge and/or person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care. The HHS report entitled *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*, the HHS Secretary's Advisory Committee on Genetics, Health, and Society identified the need for CDS tools as an important to realizing personalized pharmacotherapy.

CDS has been leveraged for many decades now to improve clinical decision making related to traditional medical interventions and when compared to other approaches to improve practice, CDS has generally been shown to be more effective and more likely to result in lasting improvements in clinical practice. However, an interim report from an ongoing RAND study indicates that none of the commercial electronic health record systems currently provide CDS to support genomic medicine. Thus, it appears that the CDS might be an important aspect of the delivery of information for clinical decision-making; however there has been little research or investment in CDS to optimally deliver information to healthcare providers to support practice of PHC.

The nuances in clinical decision-making in PHC already render many care scenarios complex. Access to an EMR and the ongoing codification of medical knowledge (i.e., Clinical Practice Guidelines or CPGs) will be essential to addressing this growing translational gap. CPGs greatly facilitate, but are not sufficient for translating knowledge to practice. Almost 2000 active CPGs exist in the US National Guideline Clearinghouse<sup>56</sup> and an individual CPG may encompass dozens to hundreds of clinical recommendations. These recommendations will rapidly expand in the era of genomic and personalized medicine, and thus codification of knowledge will be essential to increasing its access. EMRs offer a platform to translate codified knowledge into real-time actionable processes. Genomic data will need to be accessed with other patient data located in disparate locations within the EMR and evaluated in relation to a rule set. Real time actionable recommendations and CDS will need to be created and supported by an integrated and intuitive visual display of information.

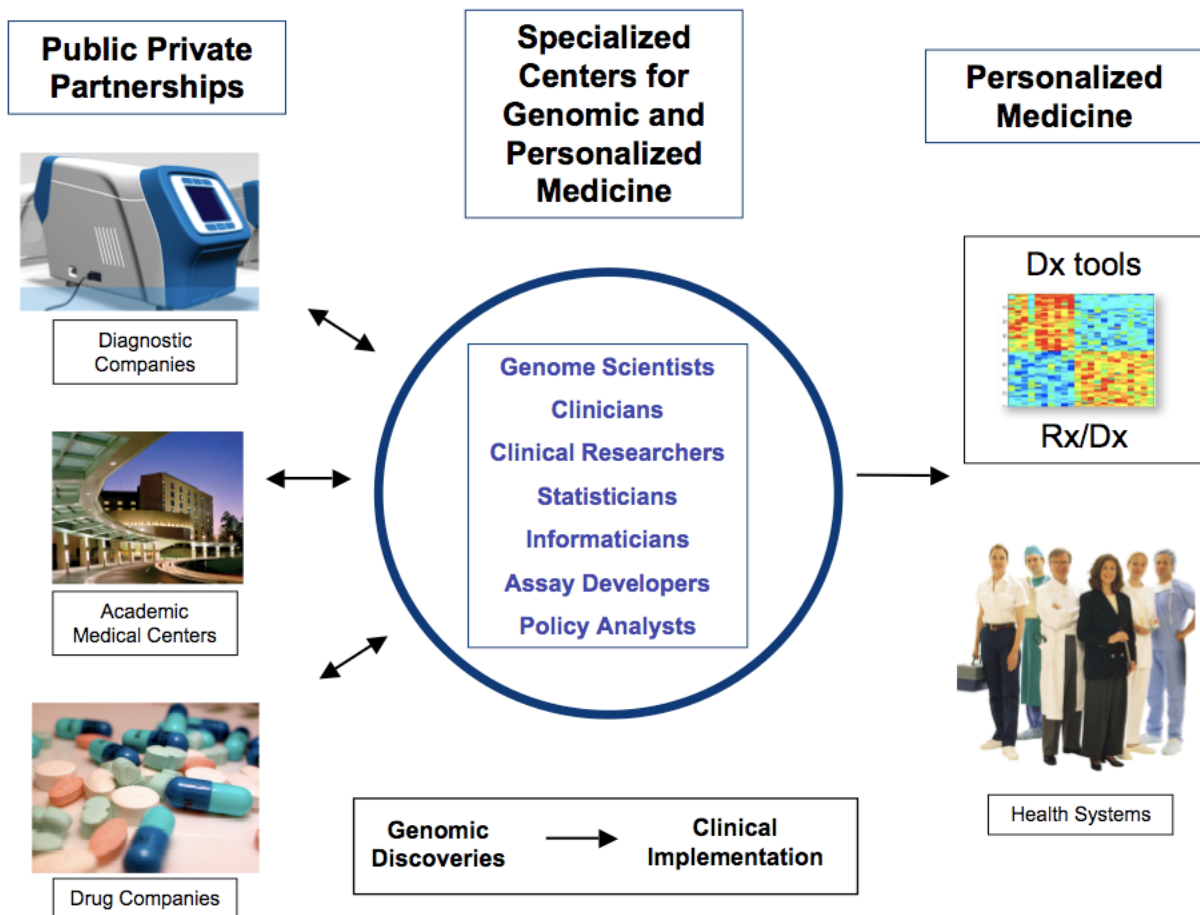
The EMR also offers an exciting opportunity for population and health outcomes (T4) research. It represents an economically efficient means of obtaining phenotypic data and biosamples for generating genotypic data and for validating discovery data as well as assessing public health impact of these discoveries on long term outcomes. The EMR thus represents a potentially large increase in efficiency for obtaining phenotypic data and can also be an extremely efficient tool for patient recruitment and biosample acquisition. The data federation initiated by the HMO Research Network (HMO RN) offers an example of a venue for the type of outcomes research needed to provide evidence that a PHC strategy will provide value. The network is a consortium of 15 research centers, each affiliated with a non-profit integrated health care delivery system, all of which have or are developing ambulatory care EMR systems. In addition to the development of best practices for research administration for multi-site collaborations, the HMO RN has initiated efforts to establish a Virtual Data Warehouse (VDW), to simplify data sharing among network participants. We encourage partnerships between AMCs and networks such as the HMO RN and mechanisms to fund them such that these data can be obtained expeditiously.

#### **Payors as integrated partners in T3 and T4 research.**

As indicated above, by sharing data and coordinating their efforts it may be possible for AMCs/health systems, payors, and diagnostics companies to study the penetration, dissemination and implementation of new personalized health tools and their effect on

health outcomes<sup>57</sup>. This, of course, would even more powerful if common standards of reporting from EHRs were possible across health systems. The NIH's Clinical and Translational Science Awards program that seeks to fund 60 centers of translational research as a consortium by 2011 may provide the foundation of infrastructure and standards required to begin to address these issues across AMCs as has been done by the HMO RN. This may be an opportunity for any national agenda for PHC to leverage the investment and emerging architectures in that program that span the breadth from the laboratory to the community. With open access to data, scholars and policy makers could determine the factors that affect clinical uptake and the resulting economic and health impact. It would be difficult for any of these parties to make these determinations independently in a reasonable timeframe.

Early examples of these novel partnerships are beginning to emerge. For example, the Mayo Clinic has partnered with Medco to evaluate test results from over 1,000 patients taking Warfarin. In another example, Kaiser Permanente of California partnered with Genomic Health and USC's Keck Medical School to underwrite a study of the clinical utility of Oncotype DX within the Kaiser Permanente coverage population<sup>58</sup>. In each case, the payor has been willing to sponsor additional clinical research when prior published research indicated both clinical validity and a potential to save costs and the test was already commercially available to test. However, these opportunities are relatively rare as few diagnostic programs have the resources or long history of use to provide the preliminary support.



**Figure 3: Specialized Centers for Genomic and Personalized Medicine.**

### **A Call for Specialized Centers as Catalysts Accelerating Genome Information to Medicine**

AMCs, while well positioned to discover and develop new tools, lack the resources, infrastructure, and skills to bring new personalized health discoveries into the market place and ultimately into clinical environment. By contrast, diagnostic companies typically have the infrastructure to make tests widely available: high-volume regulatory-compliant labs, sample collection and tracking, regulatory expertise, relationships with payors, marketing and physician education capabilities, but often lack the resources to mount an effective research and development effort to create the “content” for new diagnostic tests. Through intellectual property licensing and sponsored research agreements, academia and industry have shown that they can form synergistic partnerships to advance personalized medicine. However, even with their combined skills and resources, it has proven extremely difficult to navigate a personalized medicine program through the entire “translational continuum”. At the same time, payors are motivated to see effective models of PHC implemented and have the infrastructure and access to longitudinal data to contribute to important research on diffusion and community health impact.

Specialized centers for genomic and personalized medicine in AMCs – perhaps modeled programmatically after the Centers for Excellence in Women’s Health Program at the



NIH – can be instrumental in integrating, facilitating and catalyzing the needs of government, academic and industry stakeholders by providing:

- 1) access to patients, patient data, and molecular and biological data that drive the development and exploration of genomic information and its link to clinical outcomes
- 2) the scientific foundation for novel biomarker discovery for both disease and drug response based on mechanism
- 3) an environment for innovation that fuels the development of novel translational strategies
- 4) a vehicle for aligning the efficiency and quality metrics of patient care with the goals of personalized medicine
- 5) a network for defining, validating and implementing common data standards to facilitate knowledge sharing and accelerate discovery, validation, and monitoring of new PHC tools,
- 6) the infrastructure for the types of public-private partnerships required for executing genomic assay guided clinical trials, and finally
- 7) a place to engage in a dialogue and research on the key issues challenging the translation of genomics into PHC: education, facilitating clinical trials, regulatory policies, information systems, research on dissemination, and integration into practice.

Currently there are no structured programs in genomic and personalized medicine. Several institutions have made the commitment (Duke University, Vanderbilt, Harvard, Johns Hopkins, University of Utah, Ohio State University) but none has done so with federal support. Moreover, the tasks required, we would argue, are larger than that any single AMC can tackle. To bring about the transformation in health care the genome has promised will require assembling diverse stakeholders focused on the application and translation of genomics with a goal of improving the health of individuals and driving efficiency in health care. These centers will thrive on their interdisciplinarity. Specialized centers housing basic genome science laboratories, clinical researchers, informaticians, clinicians, economists, health policy makers and in partnership with industry (pharmaceutical and diagnostic companies), and with health systems that will enable the scientific output of the genome to cross the chasm between bench and bedside. A series of Centers that focus on specific aspects of the challenges that learn and participate with one another would, in our opinion, be a major step forward in developing and enabling the continuum of strategies required for the fullest impact of genomic and other relevant information on PHC.

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# **Personalized Medicine and Disruptive Innovation: Implications for Technology Assessment**

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## **ABSTRACT**

The fulfillment of the promise of personalized healthcare will likely require not only technology innovation but the adoption of new business and organizational models to allow for the new technologies to take hold in a disruptive fashion. At the root of the problem lays the question as to whether we have the right public policies and private strategies to allow for innovation to take hold in the healthcare arena. The current paper discusses a framework for considering this question, and proposes potential policy solutions to enable the adoption of technologies to yield improvements in both quality and costs.

## **The Promise of Personalized Medicine**

New technologies offer the potential for revolutionary changes in the practice of medicine, from molecular diagnostic tests that detect disease before symptoms are evident to patient profiling techniques that help predict which patients are most likely to benefit from or be harmed by specific therapies. These approaches and the extensive data they require will need to be supported by a new information architecture. This system has been described as personalized health care—treatments and services targeted to the specific biology of the individual, leading to potentially significant improvements in patient care. Although this vision has been articulated for several years, researchers are slowly gathering the information required to support the adoption of specific technologies that will be the crucial building blocks of the system. Other aspects of this vision are less developed, and the investment theses required to bring new technologies to market remain speculative.

At the policy level, there are recurring questions of the correct approach to innovation in health care. Do we have the right public policies and private strategies in place to foster innovation in the health care system? At the core of these discussions is a question of whether personalized health care will require a new approach to technology assessment and dissemination, one that embraces the tremendous potential of the vision of

personalized medicine. What is the role of technology innovation in health care, and what should be the public policy responses to innovation?

### **Technology and Innovation in Health Care**

Technology development and diffusion can offer new opportunities for patient benefit. In assessing the role of technology innovation, one field of scholarship has explored the relationship between technology innovation and organizational innovation. This line of inquiry presents a useful framework for discussions of the broader policy questions related to personalized medicine.

New technology often is accompanied by new business models. In competitive markets, innovation in technology enables new business models to use the advances of the new technology to offer cost or quality advantages to the end user. When successful, these new combinations of technology and business strategy are able to supersede their predecessors.<sup>1</sup> This issue has been examined in detail by Christensen,<sup>1</sup> who assessed the relationship between technology innovation and organizational innovation in the computer disk drive industry.

Christensen's concept of "disruptive innovation" begins with an assumption that consumer demand for a given technology is normally distributed, with the tails of the consumer preference curve representing high-end users with specific needs and price insensitivity and the low-end users with limited needs and price sensitivity. Firms already in the marketplace offer their products to all users but develop their technologies to meet the needs of the high-end users, their most valued customers. High-end users are thought to be the most profitable consumers and to be the most articulate about their needs. To satisfy the demands of this group, firms improve their technologies over time within the constraints of an existing business model, an approach Christensen termed *sustaining innovation*. The resulting products and services target the needs of the most lucrative segments of the market.

Christensen's key observation is that so-called sustaining innovation leads firms to develop products that possess capabilities far beyond the needs of the average consumer. This strategy creates opportunities for new firms to enter the market with new technologies and business models that focus on the more limited needs of average consumers. When successful, these new firms can supplant the existing firms in a process called "disruptive innovation."

There are many examples of disruptive technologies. One includes digital photography, which was disruptive to photographic film, as initial digital cameras had worse picture quality than traditional film and the computer tools available to edit and share photos were still in their infancy. However, the convenience of digital photography grabbed a new market niche, and soon the quality of digital photography improved and in many ways surpassed film photography. Other examples include minicomputers, which were a disruptive innovation to the mainframe market; personal computers were in turn a disruptive innovation to the minicomputer market. Mobile telephones were disruptive to fixed-line telephones. This dynamic process of firm entry and firm exit from markets

offers tremendous potential benefits to consumers over time in terms of reducing costs and improving the quality of products and services available in the marketplace.

### **Disruptive Innovation in Health Care?**

In the health sector, it is difficult to identify examples of truly disruptive technologies. Some have argued that home glucose monitoring, coronary angioplasty, and the nurse practitioner model are examples of disruptive innovations in health care.<sup>1</sup> However, none of these technologies has been able to fully disrupt the market. None has fundamentally changed the system of primary care or fostered the development of new and innovative models of health care delivery.<sup>1</sup> In most cases, these innovations have been unable to develop into the type of disruptive innovations we see in other markets when the new replaces the old.<sup>1</sup> Instead, technology has generally added to existing systems in the manner of sustaining innovation.<sup>1</sup> Physicians have fought the entry of the nurse practitioner model, and payment regulations restrict nurse practitioners to a primary care role.<sup>1</sup> The business model to offer a real-time interface between home glucose monitoring and the physician office has taken years to evolve.<sup>1</sup> Furthermore, angioplasty relies on the same hospital-based model as cardiac surgery; the procedure is simply performed by a cardiologist instead of a cardiac surgeon.<sup>1</sup>

In short, there is a lack of solid examples of disruptive innovation in health care. It is not difficult to discern why this might be the case. The health care industry exists through a relationship between business and government that is different from the computer disc drive industry that Christensen observed. These interactions, in the form of regulations, professional standards, and administrative procedures, create opportunities for incumbents to support the status quo by erecting barriers to market entry. The typical firm bringing a disruptive innovation to market is unable to meet these established rules, since it characteristically offers products or services with a narrower or more limited scope, a different business model and potentially a different customer focus from that of incumbent firms. An unintended consequence of this system is an environment that supports sustaining innovation over disruptive innovation. The health care market does not have the advantage of disruptive innovation to drive cost and quality improvements in the marketplace.

### **Administrative Barriers to Innovation**

We have previously proposed the adoption of the definition of regulatory controls (“regulations”) offered by Berenson<sup>1</sup>. Further, we have adopted this framework for both the public and private regulators in the healthcare market as administrative barriers. Regulation has the effect of developing a set of rules and standards for a market, including rules governing market expansion and a process for firm entry into a market. Regulations in health care include the governance of third party payments in health insurance<sup>1</sup> a medical liability system based on the standard of care, or rules on hospital markets (certificate of need requirements). As we discussed above, new entrants may not meet these administrative criteria or may not be able to navigate this process. As a result, all of these regulations may inhibit entry of new business forms.

Market entry is a dynamic process. Given an equal opportunity, entry will be greater when profit opportunity is greatest and barriers to entry are lowest. Given the high cost



of most services in health care and the inherent profitability of the system, the health care market should be an attractive opportunity for firm entry. Also, given the quaternary care model rampant in the marketplace, existing firms have developed capacity that outstrips the needs of most consumers (and have failed to provide the front-end services demanded by most consumers). So the lack of entry should not be ascribed to a lack of interest in the market by investors.

There is a constraint on entry in this simple model—the cost of entry. The cost of entry can be seen as the cost of complying with administrative processes to create a new business model, or the cost of complying with regulatory standards that require entrants to achieve the same form or capabilities as incumbents to enter the market. These requirements can increase the cost of entry to the point where entry is no longer attractive to new firms.<sup>1</sup> Alternatively, these factors may alter the risk of any investment by increasing uncertainty regarding approval of a new business model.

The relative lack of firm entry has consequences throughout the health care marketplace, on both incumbents and new entrants. In the absence of new market entrants (or a viable threat of entrants), organizational innovation of existing firms lags or disappears.<sup>1</sup> This lack of organizational innovation on the part of incumbent firms compounds the cost and quality consequences of firm trajectories comprised of sustaining innovation on the marketplace.

### **The Policy Maker's Role**

This discussion has emphasized the potential negative consequence of current regulatory and governance practices on the health care marketplace. Clearly, regulations serve an essential role in the healthcare system<sup>1</sup>. However, by establishing a threshold above average consumer performance expectations, regulations may also preclude quality-enhancing, lower-cost innovations from entering the market. What can policy makers do to promote innovation and allow for these new technologies to enter this regulated marketplace? Another way of framing this question is, how should we take account of the negative externalities of a regulatory scheme on the marketplace?

One simplistic framework would suggest we should support adoption of disruptive innovations over sustaining innovations. This approach is clearly supported by the theoretical framework, but it contrasts with current technology adoption models, in which most technologies that reach the market are simply sustaining innovations that “add on” to existing technologies. For example, greater availability of angioplasty is now associated with more revascularization procedures per population among people older than 65 years<sup>1</sup>. Similarly, the availability of more magnetic resonance imaging (MRI) units does not reduce the number of computed tomography (CT) scans performed.<sup>1</sup>

Supporting disruptive over sustaining innovations is not a simple task. Disruptive innovation is not a result of technology innovation; rather, it is a combination of business and technology innovations. It is unclear from an assessment of a technology itself whether the business model is one that offers the potential for disruption. Second, although many products purport to be disruptive innovations, true disruptive innovations can only be identified in arrears when markets have changed as a result of the

innovations. Even with these limitations, however, potential pathways forward could emerge.

First, not all types of innovation are, or should be, of equal interest to policy makers. In most markets, sustaining innovations are ones that enter the market continuously. New versions of Microsoft Windows and new models of the Apple iPod come to market with greater capabilities than previous versions at equal or lower prices. From this perspective, the regulatory approach could be one that expects sustaining innovation as a condition of remaining on the marketplace and limits the financial rewards to products or services over time. For example, imagine if we lowered the price for an MRI each year based on an index of computer costs in the broader marketplace.

The treatment of potentially disruptive innovations, however, could be considered quite differently. In the health care environment, disruptive innovations face tremendous uphill battles, with new combinations of technology and business models that have not previously existed. Based on the theory presented to this point, regulators could consider facilitating entry of these firms and technologies as a means of enhancing the price and quality of health care services for consumers. At the same time, regulators should curtail these incentives for firms and products that do not prove to be disruptive. This suggests that broader regulatory reform would accomplish the former goal of allowing access but at the expense of many sustaining innovations benefiting from the new framework. An alternative would be a time-dependent facilitated pathway for market entry that is unique to the regulatory framework we have constructed for health care. For example, policy makers could determine a mechanism to identify technologies with potential to become disruptive and to allow these technologies to enter the market in a disruptive fashion.

### **Exploring Potential Policy Options**

One such mechanism would be the creation of an Office of Personalized Medicine (OPM) charged with reviewing new technology applications to determine if they have the potential to become disruptive. With data and business cases presented by the owners of the technologies, the OPM would assess the ability of an innovation to transform health care delivery and treatment and to eventually lead to improvements in both outcomes and cost. Such a review mechanism would encourage technology owners to think beyond the novel characteristics of their proposals to consider early on other important business and operational features that would eventually determine if an innovation goes beyond being sustaining to become truly disruptive.

For innovations deemed disruptive by the OPM, policy makers could play an important role in providing incentives for these technologies to successfully enter the market. Owners of disruptive innovations could receive vouchers for accelerated review, or the innovations could command a premium in reimbursement negotiations. Regulators could even define a special regulatory pathway for these technologies, with distinct market approval and reimbursement criteria that would more closely align with the characteristics of these technologies. As an alternative, regulators could carve out “safe harbors” for these technologies, giving the owners of such innovations flexibility and time to change the prevailing business models in their sector. Following a model similar to “coverage with evidence development” (CED) in the Centers for Medicare &

Medicaid Services (CMS), innovations considered disruptive could be subject to special reimbursement mechanisms for a given period of time, altering the prevailing incentive system in the market place and enabling the new technology to take hold. For example, under the current encounter-based reimbursement system, health care providers have little incentive to acquire technologies that enhance service but reduce the number of encounters at the clinic, because such innovations would likely result in reduced revenues for the provider. Under a “safe harbor” mechanism, health care providers who use an OPM-labeled disruptive technology to remotely monitor patients would likely be able to bill for the informal communications that such technologies would generate (eg, e-mail consultations, phone conversations).

**Example: The Complex Development Path for a Potentially Disruptive Innovator**

One clinical application for personalized medicine is targeted therapy for individual patients.<sup>1</sup> The potential implication of this approach is to offer improved safety and efficacy for individual patients<sup>1</sup> and have an immediate economic impact by avoiding therapies with low potential to be efficacious (although one would expect manufacturers to respond to this technology in terms of development and pricing strategies over time).

Currently, the regulatory pathway for development of diagnostic tests for personalized medicine applications is controversial depending on whether the test or the information from the test kit are the product. A company seeking approval for a novel molecular diagnostic test for which the test kit is being marketed requires approval from the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA).<sup>1</sup> CDRH classifies devices into three regulatory classes based on the anticipated use of the technology and the inherent risk. The class assignment determines the requirements for approval as well as the complexity of the marketing approval process (either premarket notification or the more stringent and lengthy premarket approval).

Alternatively, in vitro diagnostic devices can be developed and marketed under the Clinical Laboratory Improvement Act (CLIA) of 1988, which governs “laboratory-developed tests” (ie, tests performed in a single site where the test kit is not marketed; samples can come to the laboratory for this service from anywhere in the country). CLIA establishes three categories of testing on the basis of the complexity of the testing methodology: waived tests, tests of moderate complexity, and tests of high complexity. Laboratories performing moderate- or high-complexity testing must meet requirements for proficiency testing, patient test management, quality control, quality assurance, and personnel. However, CLIA-governed tests do not require FDA approval.

The distinction between these two separate pathways has created a special area of controversy for personalized medicine. Using gene expression technology, scientists have reported an ability to classify patients based on risk of disease recurrence.<sup>1</sup> Although the technology is in its infancy, the FDA has raised concerns about the regulatory pathway for in vitro diagnostic multivariate index assays (IVDMIAs). These devices combine the values of multiple variables using an interpretation function to yield a single, patient-specific result that is intended for use in the diagnosis of disease, or in the cure, treatment or prevention of disease; and they provide a result with a nontransparent derivation that cannot be independently derived or verified by the end user.<sup>1</sup>

Most IVDMIAs in the market are laboratory-developed tests marketed through the CLIA route, that is, tests developed by a single clinical laboratory for use in that laboratory alone. Given the strategy of not marketing the test kits and performing the tests at a single site, these tests did not fall within the scope of lab tests over which the FDA had generally exercised enforcement discretion. Concern over this space has led to a proposal to begin regulation of this market by the FDA, with the issuance by CDRH of draft guidance in July 2007.<sup>1</sup> This regulatory issue has not yet been resolved.

In addition to regulatory approval, companies seeking to enter the market with new molecular diagnostic tests also must work with CMS to obtain reimbursement for their products. This separation of approval and reimbursement results from the different missions assigned to both FDA (approval) and CMS (reimbursement). FDA approval is based on meeting statutorily defined criteria of safety and effectiveness, and literally provides permission to market a product in the US. Implementation of these criteria varies by product category, but serves as a minimum set of criteria for entry into a market. FDA review and approval is not an assessment of value, uniqueness, nor a recommendation for use or funding of a product or technology. CMS review, on the other hand, is based on a statutorily defined standard of “reasonable and necessary” for the treatment of illness or injury. This standard for reimbursement is an assessment of whether a technology should be used in the care of Medicare beneficiaries. It is a relative standard and can be influenced by the existence of an unmet medical need, the existence of comparative therapies and the value of a new technology. In principle, the separation of approval and reimbursement provides an easier entry to the market for a technology (approval), and allows the sale of a product even if there is no reimbursement by CMS for the technology.

The CMS reimbursement process itself is a complex one. The process governs three key issues—coverage, coding, and payment.<sup>1</sup> As we mentioned above, to be covered by Medicare under the Social Security Act, the new technology must be “reasonable and necessary” for the treatment of illness or injury; however, technologies that are predictive may not meet this standard since prevention is not considered medical treatment. Second, as medical claims processing has become automated, assignment of specific codes for new medical technologies has taken on a unique importance in the reimbursement process. If specific codes are not available for a new technology, payment for the technology cannot be differentiated from previous technologies. Finally, payment schemes in Medicare can vary from bundles (inpatient DRG payment) to specific (outpatient laboratory testing). When the technology will be reimbursed separately, a payment rate must be established.

Coverage, coding, and payment decisions are not necessarily made in any particular order, and the decisions can span a 12-month period. To add to the complexity, different components of CMS are responsible for different aspects of these decisions. The Office of Clinical Standards and Quality oversees national quality initiatives and includes the Coverage and Analysis Group and its three divisions, which are responsible for developing national coverage policy. Payment and coding decisions are developed by the Center for Medicare Management, with two groups and ten divisions potentially involved

in the process. In addition, there is the possibility that different regional decisions can be made about these issues in the absence of a national decision.

In recent years, CMS has shown an awareness of the need to streamline this process and has taken several steps aimed at improving it. In 2004, the Council on Technology and Innovation (CTI) was established under the Medicare Prescription Drug, Improvement, and Modernization Act to serve as a coordination point for new medical technologies. In August 2008, the CTI published the *Innovators' Guide to Navigating CMS*<sup>1</sup> to assist stakeholders in understanding the processes used to determine coverage, coding, and payment. While serving to help technology developers understand the CMS process, the CTI group is not an expedited pathway to market for new technologies.

CMS has launched several demonstration projects to test innovations in reimbursement policy. For example, the CED policy provides an abbreviated pathway to Medicare coverage while still requiring further evaluation of a new technology. At the same time, CMS is working to make coding processes more efficient and has implemented a number of initiatives to reform one of its major coding systems, the Healthcare Common Procedure Coding System (HCPCS), while moving to replace the *International Classification of Diseases, Ninth Revision*, with the more flexible and clinically relevant *Tenth Revision*.<sup>1</sup>

### **A Way Forward for Disruptive Innovations**

While these actions are steps in the right direction, a broader approach could help accelerate the access of disruptive innovations to the market. The OPM could play a significant role as a unifying and coordinating agency, acting as the single point of contact through the Department of Health and Human Services for technologies deemed disruptive. The OPM would help expedite the approval process by expertly understanding all the potential pathways involved and by helping the technology navigate the regulatory mesh. In this role, the OPM would act as an ombudsman for disruptive innovations that are seeking market approval. As described above, this process would not be open to all potential innovations but rather to those that, based on the technology characteristics and the proposed business model to implement them, are considered to have disruptive potential.

The consideration of disruptive potential would only be granted for a fixed period of time. If after such period the technology fails to deliver its disruptive promise and its novel business model fails to take hold, the OPM could elect to levy some penalties on the company, either monetary (to payback the competitive advantage gained through early market entry) or other (such as closing the OPM pathway for future innovations from the company for a given period). The intent is to make the penalty significant enough that companies will exercise best efforts to deliver on the disruptive promise of their innovations.

The OPM could build on these changes and work in tandem with the Council on Technology and Innovation, as well as the CMS Office of Research, Development and Information. Close communication between these groups would ensure tight coordination through the regulatory and reimbursement approval processes. The OPM

could also work with these groups to expand current initiatives and create new, larger demonstration projects or safe harbors for disruptive innovations. The OPM would also have to follow a strict timeline to ensure a speedy decision about whether a technology will meet the OPM standard.

Much of this policy assessment has focused on the unique role of the Federal government in the health care marketplace. Private health plans often adopt much of their coding infrastructure from Medicare and can select to follow Medicare in coverage decisions. Thus, efforts to adopt these policies by the public sector will have effects on the private sector, as well. Creating transparency in the rationale for OPM decisions and communicating the results of evaluation of technology implementation can also help to shape decisions in the private sector. Separate study of the role of the private sector in fostering disruptive innovation merits further consideration.

### **Conclusions**

Personalized medicine offers the potential for revolutionary change in the practice of medicine. It also provides a unique window into the relationship between new medical technologies, new business models for health care delivery, and the role of government in this unique marketplace. Using personalized medicine as a test of disruptive innovation in health care, we find the need for a different approach to these technologies in order for them to achieve their full potential. Achieving this result, however, is fraught with difficulty, as disruptive innovations are deemed truly disruptive only in arrears. Thus, our approach offers the potential that designations of a technology as potentially disruptive would provide competitive advantages to products or services that may not merit this consideration. A robust framework for continuing assessment (and the potential for penalties on misrepresented technologies) might help protect the integrity of this process. However, the benefits of unlocking the health care market to disruptive innovation seem to be worth the risk.



# **Assessing Risk and Return: Personalized Medicine Development And New Innovation Paradigm**

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## **Introduction**

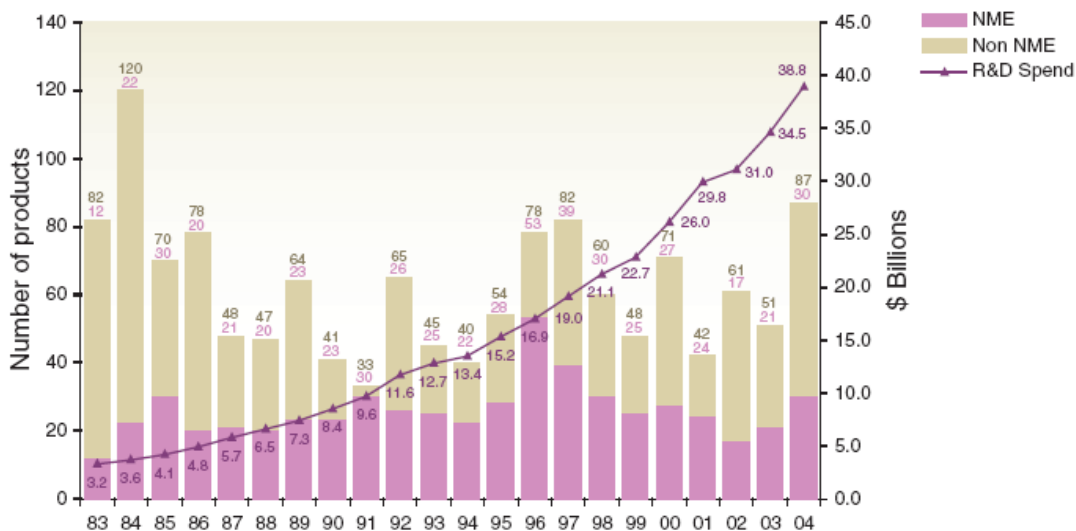
In making a credible business case for investors and industry stakeholders to view personalized medicine as a viable business model, we not only must create excitement in the promise of personalized medicine, but also must find viable alternatives in addressing the barriers or risks surrounding the biomedical discovery and development models of today. Some of the risks we identify include IP issues, difficulties in validating targets, ability to rapidly achieve proof of concept, navigating the famed “Valley of Death,” and inefficiencies in the current clinical development process, as well as the need for new industry business models that predict an attractive return on investment. In this paper; however, we limit our discussion to the potential for personalized medicine to create efficiencies in the preclinical and clinical phases of drug innovation and generate economic returns. We also introduce unique industry collaboration mechanisms with nonprofit disease-focused organizations that serve an important role in de-risking aspects of drug discovery and clinical development in their respective disease sectors, as well as bridging early-stage funding needs. These collaborations and de-risking strategies could provide an important model for the further development and growth of the personalized medicine sector.

With respect to definition, we shall use the more general term “stratified medicine,” of which personalized medicine is the individualized member of a spectrum that includes empirical medicine, stratified medicine, and personalized medicine.<sup>1</sup> In the latter two, a biomarker is critical in identifying sub-populations or strata of patients that can benefit from a therapeutic intervention that is related to that biomarker, or develops a therapy that specifically benefits an individual who possesses that biomarker.<sup>1</sup> A biomarker also may identify strata of patients that might be susceptible to side effects from a particular therapy.<sup>1</sup>



## Current Challenges in Productivity and Investment Returns

The increasing interest and excitement over the promise of stratified medicine is based on the promise of genomics, proteomics, and metabolomics to enable the researcher to identify genes and gene products that are relevant for disease, and to instruct the creation of the best therapies for patients with the respective diseases or side effect susceptibilities.<sup>1</sup> This comes on the heels of the biopharmaceutical industry struggling to meet the increasing demands on its R&D investments while facing declining levels of productivity and innovation, and loss of revenue due to patent expirations. More than three dozen drugs are losing patent protection between 2007 and 2012, with an anticipated \$67 billion loss in sales for the large pharmaceutical companies to generic competition.<sup>1</sup> The industry has responded with pharmaceutical companies increasing R&D spending by 160 percent—from \$15 billion to \$39 billion from 1995 to 2005—and with similar increases in the biotech industry, with a 150 percent increase—from \$8 billion to \$20 billion—in R&D spending during the same period. Meanwhile, submissions for regulatory approval of new drugs and therapeutic indications declined from eighty-eight in 1995 to forty-four in 2004.<sup>1</sup> Innovation in the sector also is continuing to decline, with only seventeen new molecular entities (NME) and two biologics approved in 2007, at a cost of \$2.5 billion per NMEs approved,<sup>1</sup> which is the lowest innovation-to-productivity level since 1983, when twelve NMEs were approved at a cost of \$266 million per NME.<sup>1</sup> (See Figure 1.)



**Figure 1:** A comparison of biotech and pharmaceutical R&D productivity. Source: Parexel’s Pharmaceutical R&D Statistical Sourcebook 2005/2006; Defined Health Analysis. NME, new molecular entity.

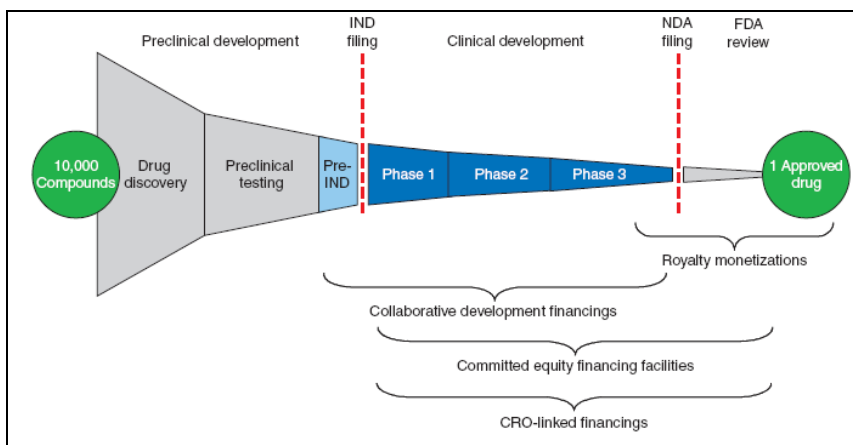
The decline in productivity and innovation has increased M&A and partnering activities among large biopharmaceutical companies at a record high in the last few years, with \$150 billion generated through M&A transactions in 2006 and \$22 billion in partnering deals for the same period.<sup>1</sup> The strategy of focusing on a few drug candidates from their combined pipelines, with a focus on producing several “blockbuster” drugs that will generate at least \$1 billion individually in peak annual global sales and be marketable to fifteen million patients or more, has not improved their productivity levels, resulting in

increased delays in development time/costs and increasing cancellations of projects at later stages of development.<sup>1</sup> Additionally, increasing regulatory pressures to conduct more lengthy and complex trials has added to the current \$1 billion<sup>1</sup> in drug development costs, of which half are attributable to the time value of money—that it takes eight to twelve years to get a drug to market.<sup>1</sup> It is also the case that, even after a drug is marketed, 70 percent of the approved drugs do not meet or only match their R&D costs.<sup>1</sup> Thus, with lower efficacy levels (40 percent to 60 percent) of most blockbuster drugs,<sup>1</sup> as well as some high-profile successes of stratified medicines such as Genentech’s Herceptin and Novartis’ Gleevec, the industry is beginning to realize the deficiencies in the economics of the blockbuster business model, which is one of the drivers of increased interest and investment in the development of stratified medicine.<sup>1</sup>

### **Early-Stage Funding Challenges in Stratified Medicine Development**

The identification of clinical biomarkers or diagnostics linked to gene expression profile of individual or sub-populations of patients is an essential feature of stratified or targeted medicine. This type of research attracts and often is best pursued by small biotech companies. One of the main challenges for these companies lies in the lack of early-stage funding to translate new discoveries into the clinic and, ultimately, to commercialization. With a narrowing access to public capital and venture capitalists increasingly reticent to invest in early-stage technology companies, smaller biotech companies increasingly are engaging in alternative financing mechanisms that often compromise their value in terms of access to future returns.<sup>1</sup>

Various alternative financing mechanisms, including partnering and out-licensing, sale of royalty streams, and Contract Research Organization (CRO) financings, all include investment capital in exchange for future royalty rights or equity shares in the biotech company.<sup>1</sup> Other innovative financing mechanisms do exist, such as collaborative development financing (CDF), where an investor provides capital and clinical expertise in exchange for licensing of a company’s pipeline, while the company maintains the “exclusive right to reacquire the drugs,” at prices determined at the time of the agreement.<sup>1</sup> An example of a CDF arrangement is the 2006 Symphony Capitol and Isis Pharmaceuticals (“Isis”) collaboration,<sup>1</sup> where Isis received \$75 million to continue the development of its cholesterol-lowering (Phase II) and diabetes drug products (two in pre-clinical) and agreed to an exclusive purchase option for its products at an “annual rate of return that averages 32 percent and is 27 percent at the end of the anticipated” collaboration period.<sup>1</sup> In 2007, Isis exercised its repurchase option, paying Symphony \$131 million. Isis, in turn, executed collaboration agreements with Johnson & Johnson and Genzyme for the three molecules in the contract. These arrangements included upfront fees in the aggregate of \$370 million with potential milestone payments of nearly \$2 billion.<sup>1</sup> (See Figure 2.)



**Figure 2:** Alternative financing sources for biotech companies<sup>1</sup>

Most of the alternative financing mechanisms, however, are not necessarily accessible for many early-stage companies, as these companies may not have the types of products that meet the returns desired by larger companies and venture capitalists. A case in point is the lack of investment in orphan drugs or neglected disease areas. Aside from Genzyme, which has been one of the few successful orphan drug-focused companies with three drugs on the market, including a \$1 billion-a-year treatment for Gaucher, and Novartis' Gleevec, a treatment for chronic myeloid leukemia with \$2.5 billion in 2006 sales,<sup>1</sup> therapeutic discovery and development for orphan and neglected diseases often have been the bane of nonprofit foundations and patient advocacy organizations, many of whom have increasingly taken on a new role of bridging early-stage funding and development gaps in disease areas where the patient population often is less than 200,000, the FDA definition of orphan drugs.<sup>1</sup>

To uncover mechanisms by which venture capitalists and biopharmaceutical companies—whose measures of success ultimately are captured in their return on investment (ROI)—could be incentivized to participate in developing stratified medicines, we have looked at the various activities of nonprofit foundations. In our view, these foundations, whose ultimate success is in bringing therapeutics and diagnostics to their patients, increasingly are engaged in “de-risking” strategies. In some cases, their target patient populations fall within the orphan disease category. Their strategies, however, not only fill important funding gaps but also have the objective of increasing the probability of success through their support activities.

### **Venture Philanthropy—Early-Stage Funding/Proof of Concept**

Although the nonprofit foundations traditionally provide basic research grants to increase scientific knowledge in their disease sectors, some have since adopted a more investor-like approach—early-stage funding for proof of concept and target validation, as well as project management support and access to their network of scientific experts and research clinics critical in translating discoveries into the clinic.

One example of nonprofit disease organizations that provide early-stage funding for proof of concept and target validation is the Muscular Dystrophy Association (MDA). Through its Translational Research Program (TRP), MDA's approach is to stratify its

patient population based on various sub-sets of the disease, including Duchenne Muscular Dystrophy (DMD), Myotonic Muscular Dystrophy (MMD/DM), Fascioscapulohumeral Muscular Dystrophy (FSHD), Spinal Muscular Atrophy (SMA), Pompe Disease, and ALS, and seek to develop targeted therapies for the sub-patient populations.<sup>1</sup> Of the \$32 million in MDA’s 2007 annual R&D budget, \$6 million was dedicated to its largest collaboration effort with ALS Therapy Development Institute (ALS-TDI), a nonprofit corporation, and \$7 million was dedicated to industry collaborations.<sup>1</sup> Muscular Dystrophy Association’s TRP provides four types of funding mechanisms for the industry—IND Planning Grant, Clinical Research Training Grant, Infrastructure Grant, and Corporate Grant—to catalyze early-stage development leading up to INDs and Phase I/II clinical trials.<sup>1</sup> (See details of collaboration deal examples at Figure 3.)

**Figure 3:** Examples of TRP Industry Grants<sup>1</sup>

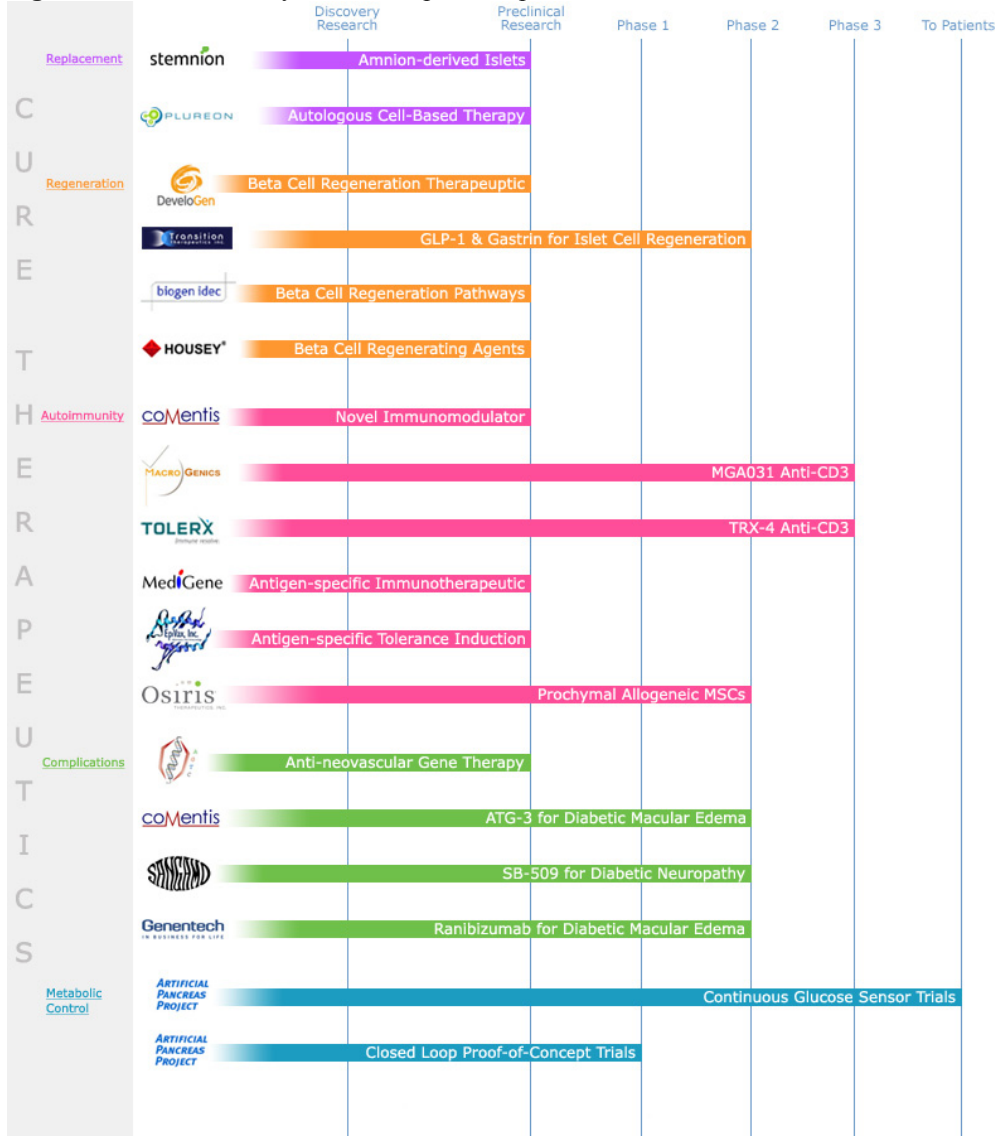
Disease Type & Company Grantees	Collaboration Description and Status
DMD/PTC Therapeutics	MDA provided PTC with an initial \$1.5 million grant, enabling the company to begin developing PTC124, a medication with the potential to treat a significant portion of patients with DMD. In July 2008, PTC entered into a collaboration deal with Genzyme, where Genzyme will provide \$100 million to PTC, with potential additional payment options, and will commercialize PTC124 outside the United States and Canada.
Pompe Disease (acid maltase deficiency)/Myozyme (approved 2006) from Genzyme	MDA provided supplemental funding of \$150,000 to cover unreimbursed costs of patients participating in Genzyme’s clinical trials for Myozyme in infantile-onset Pompe disease. In 2007, Genzyme also found Myozyme effective for older children and adults with the disease.
ALS Therapy Development Institute (ALS-TDI)	MDA is collaborating with ALS-TDI to comprehensively characterize disease progression in ALS using animal models of neurodegeneration and ALS clinical samples. MDA committed \$6 million annually for three years.

To qualify for the TRP grants, the collaborating company is required to provide matching grants and agree to a collaboration contract that includes royalty-sharing agreements and march-in rights if the projects fail to meet milestone targets. Similar to a majority of the nonprofit disease organizations, MDA neither takes equity positions in the companies with which it collaborates, nor pursues IP ownership.<sup>1</sup>

Another example of nonprofit disease organizations providing early-stage funding to industry includes the Industry Discovery & Development Partnerships (IDDP) Program of the Juvenile Diabetes Research Foundation (JDRF). IDDP’s main focus is to translate scientific discoveries into the clinic and support commercialization of therapeutics to treat type 1 diabetes.<sup>1</sup> Of its \$160 million research budget in 2008, \$16 million will be

dedicated to industry partnerships,<sup>1</sup> which is a marked change. Previously, 100 percent of its research funding went to support basic science and exploratory research within academia.<sup>1</sup> To date, IDDP has fostered twenty-four collaborations with industry, totaling \$30 million in IDDP grants.<sup>1</sup> IDDP's development partnerships are generally two- to three-year contracts, and "are intended to provide support for promising mid-stage research programs (i.e., advancement of a pre-clinical-stage program to clinical trials, or "proof-of-concept" Phase II clinical testing of promising therapeutics."<sup>1</sup> By funding early-stage testing and validation of research, JDRF's model of "de-risking" works to make it possible for its industry collaborators to advance their compounds from proof of concept to clinical development, attract additional financing, and eventually secure global licensing and marketing alliances with larger pharmaceutical companies.<sup>1</sup> By funding and providing development support of early trials through IDDP, JDRF also sees this as a way to build evidence in persuading public and private payors to cover these novel technologies.<sup>1</sup> A case in point is IDDP's collaboration with Tolerx. JDRF provided early-stage, multi-million dollar funding for proof of concept trials in both animal models and early human trials for anti-CD3 antibodies (Otelixizumab) for the treatment of early-stage Type 1 diabetes in collaboration with academic researchers in the United States and Europe.<sup>1</sup> To catalyze further development and commercialization of Otelixizumab, IDDP invested \$3.5 million in an equity stake during Tolerx's latest round of fundraising to conduct Phase II trials.<sup>1</sup> This is the first project where IDDP has taken an equity position in a collaborating biotech company. As of October 2007, Tolerx entered into a strategic alliance deal with GSK to take the antibody through Phase III trials, with a total deal value potential up to \$155 million.<sup>1</sup> Figure 4 below also exemplifies the significant commitment IDDP has made to companies to support discovery, development, and commercialization of therapeutics and devices for type 1 diabetes.

**Figure 4: IDDP Discovery and Development Pipeline**



**Venture Philanthropy and Nonprofit Venture Affiliates**

Few nonprofit disease organizations have created wholly owned nonprofit venture affiliates to navigate through the challenges of translating early-stage discoveries into the clinic or bridging the “Valley of Death.” These entities serve as catalysts on various scales, not only by providing variable funding options from annual to multi-year commitments averaging from thousands to multi-millions of dollars, but also by providing mechanisms to address the development challenges. These include: providing project management expertise and scientific, clinical, and development networks (in some cases CRO outsourcing networks) that can assist the collaborators. In terms of return on investment, most do not take equity positions in the companies they collaborate with; instead, some deals are royalty-based, in which the organizations get a multiple

back if the drug is approved and, in some cases, additional compensation for extraordinary sales results. Additionally, in cases where collaboration programs suspend due to milestone failures, some organizations obtain worldwide rights to develop the products with an agreement to negotiate royalties to the original collaborator once their investment is recouped.

An example of a nonprofit disease organization that has created unique project management and target validation mechanisms is the Multiple Myeloma Research Consortium (MMRC), a supporting organization of the Multiple Myeloma Research Foundation (MMRF). Through a collaborative contractual arrangement with its fifteen research centers,<sup>1</sup> the MMRF's strategy is to incentivize biopharmaceutical companies to collaborate on the development of new drugs and therapies. The MMRC's tri-focus on genomics and credentialing of molecular targets, validation of drugs, and its offering of multi-site clinical trial capabilities creates efficiencies that are critical in de-risking early-stage proof of concept and target validation.<sup>1</sup> One of the MMRF's strategies is to identify genetic complexities of multiple myeloma and to identify molecular targets by analyzing the MMRC's tissue bank and patient data bank on disease onset and progression, with the goal of personalized medicine development.<sup>1</sup> To assist in the process of validating new targets, the MMRC has created screening tools—including a panel of twelve extensively characterized myeloma cell lines with full genetic and biological characterization—to screen new drug candidates.<sup>1</sup> The MMRC also has funded the Multiple Myeloma Genomics Initiative, investing \$8 million in research funding over the past four years to analyze 250 patient tissue samples via gene expression profiling, comparative genomic hybridization and exon re-sequencing.<sup>1</sup> To expedite and create efficiencies in conducting multi-site clinical trials of novel and combination therapies, the MMRC has created uniform contracts, clinical trial agreements, and correlative sciences agreements.<sup>1</sup> (See Figure 5.) To further expedite the process, the MMRC provides supplemental project management to accelerate projects from protocol concept through trial conduct and provides clinical research coordinators for the MMRC members.<sup>1</sup> The MMRF sees its main function as an integrator and facilitator of research and collaboration among biopharma companies with the research centers.<sup>1</sup> Since 2003, the MMRF has helped bring four drugs to market, including Millennium Pharmaceutical's Velcade in 2003, Celgene Pharmaceutical's Thalomid<sup>®</sup> and Revlimide<sup>®</sup> in 2006, and Millennium Pharmaceutical/J&J Pharmaceutical's Doxil<sup>®</sup> in 2007,<sup>1</sup> and has supported more than thirty compounds and combinations in trials or pre-clinical studies to date.<sup>1</sup>

**Figure 5:** MMRC Clinical Trials. MMRC Trials and the year in which they have opened. A total of 15 trials have initiated in the MMRC since 2005. Abbreviations: R: Relapsed; R/R: Relapsed/Refractory; Rev: Revlimid; Dex: Dexamethasone; Vel: Velcae; IST: Investigator-sponsored trial. Unless marked as IST, all trials are company-sponsored. \*\*Trials expected to open by year-end 2008.

	Ph. I/II Novartis LBH589/Velcade	<b>Ph. II HDAC inhibitor/Velcade**</b>
	Ph. I Semafore SF1126	<b>Ph. II mTOR inhibitor/Velcade (IST)**</b>
	Ph. II Proteolix Carfilzomib (R)	Ph. I PDL Elotuzumab/Rev-Dex
	Ph. II Proteolix Carfilzomib (R/R)	Ph. I Celgene CC-4047
Ph. I Nereus NPI-0052	Ph. I Wyeth Torisel/Velcade (IST)	Ph. I PDL Elotuzumab/Vel-Dex
Ph. I Keryx Perifosine/Rev-Dex	Ph. I Ortho Tipifarnib/Velcade (IST)	Ph. I/II Rev-Velcade-Doxil-Dex (IST)
Ph. I Novartis TKI258	Ph. II Novartis LBH589	Ph. Ib Novartis LBH589/Rev-Dex
<b>2005 – 2006</b>	<b>2007</b>	<b>2008</b>

From a funding perspective, 93 percent of the MMRF's annual budget goes to research and related programming.<sup>1</sup> Of these, in 2007, the MMRF earmarked approximately \$15 million for R&D, with \$2 million allocated for direct funding to biotechs.<sup>1</sup>

One of the leading examples of a nonprofit venture affiliate is the Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), a wholly owned venture arm of the Cystic Fibrosis Foundation (CFF). CFFT's focus is to develop stratified medicine based on CF-related genetic mutations, of which there are 1,400 on a single gene.<sup>1</sup> To date, CFFT has successfully identified and is working on the development of therapies that target the basic defect of the disease, as well as those that will provide better options for disease management. Therapies that target the basic defect are based on various genetic mutations, including Delta F508, a genetic mutation present in 90 percent of cystic fibrosis (CF) patients, and G551D, which is present in 10 percent to 30 percent of CF patients.<sup>1</sup> CFFT's strategy is to invest in early-stage discovery and development. Their funding ranges from \$50,000 to \$25 million, with an average of \$2 million to \$4 million per year, with some multi-year commitments averaging \$15 million to \$20 million.<sup>1</sup> CFFT's successes in aiding drug discovery are measured in terms of increasing its pipeline, which has grown to more than thirty drug candidates.<sup>1</sup> CFFT administers the collaboration contracts based on milestone successes, with pull-out rights for failures.<sup>1</sup> It also invests in a wide range of technologies, from target identification, novel screening platforms, detection of new chemical compounds, and screening of existing compounds and drugs.<sup>1</sup> In terms of return on investment, CFF does not take equity positions in the companies with which it collaborates; instead, some deals are royalty-based, in which CFF may get a multiple back and/or a percent of revenue if the drug is approved and, in some cases, receives additional compensation for extraordinary sales results.<sup>1</sup> Should the development program suspend due to milestone failures, CFF obtains automatic



worldwide rights to develop the product with an agreement to provide some royalties to the original collaborator once CFF's investment is recouped.<sup>1</sup>

An example of CFFT's largest industry collaboration to date includes a multi-year collaboration with Vertex Pharmaceuticals, Inc. (Vertex), in which CFFT provided an aggregate of \$76 million from 2000-2008<sup>1</sup> to support the development of two compounds (VX-770 and VX-809), which target the functional restoration of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the protein responsible for the progression of cystic fibrosis. Through this collaboration, Vertex was able to develop VX-770 from discovery to Phase IIa, where it focused on how VX-770 affects CFTR protein function and clinical endpoints in CF patients with genotype G551D (affects approximately 4 percent of the 30,000 CF patient population in the United States), achieving positive interim results in March 2008.<sup>1</sup> See other examples of CFFT's portfolio in Table 6.

**Table 6:** Examples of CFFT investments

Collaborating Company	Project Description	CFFT Investment
EPIX Pharmaceuticals, Inc.	Use of EPIX proprietary PREDICT technology to create a computerized 3-D model of CFTR protein, using the model to identify sites within Delta F508 mutation of CFTR and search their library of chemical compounds for a small molecule that may work on those sites. In 2007, EPIX discovered a molecule that, in the lab, restores function to Delta F508 CFTR in cells.	\$52 million including an original \$18 M research award over 3 years and a subsequent discovery and development award over 7 years.
FoldRx Pharmaceuticals, Inc.	Use of a novel screening platform to detect new chemical compounds that could improve the function of misfolded proteins, like the Delta F508 mutation.	\$22 million over five years to use its high-throughput screening platform to discover and develop new compounds.
CombinatoRx, Inc.	Screening approximately 2,000 approved drugs individually or in combination for its impact on correcting Delta F508 in the lab.	Commitment up to \$13.8 million.
Vertex Pharmaceuticals, Inc.	Development of VX-770, its first CFTR modulator clinical compound, which entered Phase II clinical in 2007. Also developing second compound known as "correctors," VX-809.	\$76 million to date for VX-770 and VX-809.

## **Venture Philanthropy and Nonprofit Venture Intermediaries**

Few large foundations, like the Gates Foundation through its Global Health Program (GHP), utilize independent nonprofit venture intermediaries to finance and manage the discovery and development of innovative therapies for neglected diseases affecting the developing world.<sup>1</sup> GHP's goal through its venture intermediaries is to accelerate R&D and provide global access to new vaccines, drugs, and other health tools that combat infectious diseases, including malaria, HIV/AIDS, TB, and pneumonia.<sup>1</sup> The venture intermediaries serve "as a virtual pharma company looking for good ideas, progressing them to the point where proof of concept is achieved,"<sup>1</sup> and de-risking projects to the point that big pharma may be incentivized to collaborate in developing the therapies.<sup>1</sup> GHP is involved in the portfolio management of the venture intermediaries, but the intermediary conducts the project management.<sup>1</sup> To date, GHP has committed \$6 billion in global health grants to organizations and researchers worldwide, including \$200 million to Medicine for Malaria Ventures (MMV) over five years.<sup>1</sup>

The venture intermediaries, often called Product Development Public-Private Partnership (PDPs)<sup>1</sup> entities, operate globally with a focus on providing R&D funding and project management expertise in the neglected disease areas such as Malaria and TB.<sup>1</sup> MMV is one of the nonprofit venture intermediaries that the Gates Foundation and GHP funds.<sup>1</sup> MMV's role is to facilitate the discovery and development of innovative anti-malarial drug candidates into clinic.<sup>1</sup> MMV does not conduct discovery or development itself but provides financial and project management support requiring milestone achievements and quick termination rights for those who fail to meet milestones.<sup>1</sup> In return for its investments, MMV often seeks IP rights from the discovery and development projects it funds.<sup>1</sup> In projects that it funds through commercialization, MMV will often negotiate for the delivery of drugs to poor developing countries at "no profit, no loss" basis.<sup>1</sup> It also will retain the ability to license to multiple drug manufacturers.<sup>1</sup> In cases where industry partnership fails during the development phase, MMV will either take full ownership of the IP or require an exclusive, worldwide, transferable license that is royalty free in malaria endemic countries.<sup>1</sup>

In 2007, MMV invested more than \$37 million in nearly forty projects that include four projects in late-stage Phase III clinical trials and three mini-portfolios with GlaxoSmithKline (GSK) (three projects), the Broad Foundation/Genzyme (five projects), and Novartis Institute for Tropical Diseases (NITD)/Novartis (nine projects).<sup>1</sup> Clinical trials MMA supported in 2007 include: Collaboration with Novartis' submission to Swissmedic for approval of its first ACT (Coartem<sup>®</sup> Dispersible); Eurartesim<sup>®</sup> (with Sigma-Tau Pharmaceuticals, Inc.), which received orphan drug designation in the U.S. in 2006 and by the EU in 2008; and MMV/Shin-Poong Pharmaceuticals collaboration for Pyramax<sup>®</sup>. MMV has a wide platform in its collaboration with Shin-Poong, covering two pivotal trials for *Plasmodium falciparum*, trials for *P. vivax*, and also a new formulation specifically for small children.<sup>1</sup>

MMV also has engaged in identifying new targets based on the genome sequence of *Plasmodium falciparum*, the main cause of human malaria, and has collaborated with Novartis and GSK to screen their collection of compounds that may be able to kill the malaria parasite. Out of more than three million compounds tested, more than 10,000 showed interesting activities at low micromolar concentrations.<sup>1</sup> (See Figure 7.)

Figure 7: Sample MMV investments in 2007<sup>1</sup>

Collaborating Company	Project Description	Amount Invested in 2007
MMV/Novartis (Coartem <sup>®</sup> Dispersible)	Phase III trial—Development of a pediatric dispersible tablet, Coartem <sup>®</sup> Dispersible, containing a fixed-dose combination of artemether and lumefantrine. (ACT)	\$1.68 million
MMV/Sigma-Tau Pharmaceuticals, Inc. (Eurartesim <sup>®</sup> )	Phase III trial—Fixed-ratio drug combination of dihydroartemisinin and piperazine, being developed to treat uncomplicated malaria.	\$2.85 million
MMV/Shin-Poong Pharmaceuticals, Inc.	Phase III trial—Fixed-dose oral combination of artesunate with pyronaridine. The course of treatment is once a day for three days. Currently carrying out pivotal Phase III studies in <i>Plasmodium falciparum</i> and <i>P. vivax</i> patients to confirm safety and efficacy. A specific pediatric granule formulation also is being tested for safety and efficacy.	\$12 million
MMV/GSK mini-portfolio (five projects)	Engaged in five separate projects ranging from 1) development of next-generation pyridones derivative; 2) development of a second-generation macrolide; 3) identification of additional potent falcipains inhibitors; 4) high-throughput screening assay to study the effect of the entire GSK library of compounds on the growth and death of <i>P. falciparum</i> (To date, the majority of the 1.5 million compounds have been screened in a high-throughput assay, and more than 10,000 hits have so far been identified with interesting activity. The goal for 2008 is to complete the screen, characterize the hits, and use chemoinformatic technologies to cluster them.); and 5) discovery program to screen new class of compounds, namely THiQ, that showed promising activity against <i>P. falciparum</i> from its previous Fab1 project.	US \$2.2 million
MMV/Broad Institute of MIT and Harvard/	Engaged in three projects: 1) screening of the broad compound collection against	\$1.6 million

Genzyme mini-portfolio (three projects)	whole parasite assays with expansion plans in 2008 to include more compounds from the Genzyme library; 2) identification of natural products for malaria treatment; and 3) use of proteomics technology to identify molecular targets. Targets for one of the natural products have been identified, allowing it to be developed for a molecular-based, high-throughput screening (HTS) assay. Focus is to continue identifying more molecular targets that will not only be essential for parasite growth, but tractable in terms of finding small-molecule inhibitors.	
MMV/NITD/Novartis mini-portfolio (nine projects)	Engaged in nine projects ranging from early-stage research into identifying new targets for liver stages of <i>P. vivax</i> infection, through to optimization of compounds based on artemisinin dimmers. Several projects are moving forward from early-stage hits to lead compounds. One is the chemistry strategy based on successful screening of more than two million compounds from the Novartis compound collection, which led to the selection of more than 6,000 active compounds.	\$589,000

As demonstrated above, the nonprofit disease organizations are having an impact on translating early-stage discoveries to development phases, not only by providing funding for proof of concept and target validation but also by providing project management and a ready-made network of scientific and clinical infrastructures to expedite and de-risk the development of novel therapies. These approaches are instructive for developing and funding early-stage development models for the stratified medicine sector, but are only part of the picture in making a business case for stratified medicine. We also must assess the clinical trial development risks and how the nonprofit disease organizations may contribute in de-risking clinical development and its applicability to stratified medicine, which will be discussed in the next segment of this paper.

### **Risks and Impact on Return: De-risking Clinical Trials**

The critical part of assessing potential return on biomedical product development hinges on the assessment of risk factors in terms of clinical development costs, time, and success probabilities to get to market.<sup>1</sup> Although most venture capitalists and biopharmaceutical companies use their own valuation models to assess potential investment returns of biomedical products in development, a baseline industry average provides a snapshot of the development risk factors and possible mitigation strategies to employ through unique collaborative models with nonprofit disease organizations.<sup>1</sup>

### **Development Risk and Clinical Trial Design**

With increasingly complex and chronic diseases as potential targets for new biomedical innovations, the industry is continuing to face decreasing productivity and increasing clinical trial failure rates, adding to the increase in development risks in terms of cost/time.<sup>1</sup> Currently, approximately 80 percent of Phase I trials are expected to fail (i.e., they have a 20 percent chance of successfully making it to market), and 70 percent are expected to fail in Phase II,<sup>1</sup> with expected success rates from Phase III to market between 50 percent and 70 percent. New biologic molecular entities have slightly better success rates than those identified for new chemical entities.<sup>1</sup>

These tools will play a significant role in de-risking the drug development process.<sup>1</sup> Continued advancement in new genomics-based technologies and high throughput screening tools will improve researchers' abilities to discover reliable clinical biomarkers that can stratify and enable the discovery of the best therapies for patients.<sup>1</sup> For instance, use of clinical biomarkers early in the clinical trial process could help to decrease costs by identifying better responders, thereby reducing trial sample size to demonstrate efficacy and help to exclude patients early using toxicity biomarkers.<sup>1</sup> In addition, stratifying for key biomarkers early in the trial process not only creates the possibility of shortening end-point observation times, but also creates the ability to gather data to improve the compound or alter the trial design altogether early on, allowing for educated data mining to better define the appropriate patient population.<sup>1</sup> Additionally, the collection of DNA information from ongoing clinical studies, with patients' consent, also offers the possibility to accelerate future research with increased efficiency.<sup>1</sup> Shorter trials with specific results also have the advantage of expedited FDA reviews, as exemplified by FDA's review and approval of Genentech/Roche's breast cancer treatment, Herceptin, which took six months,<sup>1</sup> or that of Novartis' Gleevec, which took three months. It is anticipated that stratifying patients based on clinical biomarkers may reduce the cost of clinical trials by a factor of two to five, as it would help to narrow the test populations and commercialization time from the current ten to twelve years to five years or less.<sup>1</sup>

### **Time/Cost Correlation**

The current industry expectations are the following—in Phase I of the clinical trials, twenty to eighty healthy volunteers are given a new drug compound to test for safety at a cost ranging from \$8,000 to \$15,000 per patient with an average time period of six months to a year.<sup>1</sup> In Phase II, 100 to 300 patients are given the new drug compound to assess clinical efficacy and dosage levels at a cost ranging from \$8,000 to \$15,000 per patient, with an average time period of two to three years.<sup>1</sup> In Phase III, 1,000 to 5,000 patients are tested, often in placebo-controlled, randomized, and double-blinded trials for efficacy and overall risk-benefit assessment at a cost of \$4,000 to \$7,500 per patient. These data sets, however, do not provide a clear picture of the real drivers of time/cost correlation. For instance, key drivers of time delay in clinical trials include difficulties in patient recruitment (this causes 33 percent to 66 percent of time delay) and data management

(8 percent to 14 percent), as well as difficulty in manufacturing and regulatory/ethics approvals,<sup>1</sup> resulting in upwards of 75 percent of all U.S. trials experiencing delays of one to six months or more.<sup>1</sup> With more than 40 percent to 50 percent of per-patient costs attributable to clinical operations, including project management, monitoring, and regulatory and data management,<sup>1</sup> finding ways to mitigate delays and deploying strategies to increase efficiencies in the clinical process will be critical in decreasing risks associated with development costs/time. (See Figure 8.)

**Figure 8:** Clinical Trial Parameters<sup>1</sup>

<b>Phase I</b>
Likelihood of eventual FDA approval: 20%
Average years to completion: 0.5–1
Supporting animal studies: ~\$500,000
Number of clinical-trial subjects: 20–80
Per-subject cost: \$8,000–\$15,000
<b>Phase II</b>
Likelihood of eventual FDA approval: 30%
Average years to completion: 1.5
Supporting animal studies: ~\$1 million
Number of clinical-trial subjects: 100–300
Per-subject cost: \$8,000–\$15,000
<b>Phase III</b>
Likelihood of eventual FDA approval: 67%
Average years to completion: 3.5 years
Supporting animal studies: ~\$1.5 million
Number of clinical-trial subjects: 1,000–5,000 (about 10× the number in phase II)
Per-subject cost: \$4,000–\$7,500 (half that of earlier per-patient costs)

### **Venture Philanthropy—Clinical Trial De-risking Mechanisms**

In identifying ways to de-risk the time/cost factors in clinical development, one of the emerging models is industry collaboration with nonprofit foundations which, at varying levels, offer mechanisms to expedite and create efficiencies such as readily accessible patient registries and databases, and a broad network of clinical and investigator sites that offer scientific expertise and support.

### **Venture Philanthropy and Patient Registry/Database**

Patient recruitment in clinical trials, especially for specific disease indications, are extremely time consuming and often difficult, adding tremendously to clinical trial time/costs. One of the important de-risking mechanisms provided by the nonprofit disease organizations is access to their network of patient registries and databases. Although most organizations are at various stages of developing their patient registries, Cystic Fibrosis Foundation (CFF) has created an extensive infrastructure to serve this purpose. For instance, CFF accredits more than 115 cystic fibrosis care centers with ninety-five adult care programs and fifty affiliate programs nationwide,<sup>1</sup> creating one of

the largest patient registry databases among U.S. foundations, with information about more than 24,000 CF patients receiving care at one of the CF care centers.<sup>1</sup> CFF's database includes not only the patient contact information, but detailed information about genotypes, pulmonary function test (PFT) results, pancreatic enzyme uses, length of hospitalizations, home IV use and complications related to CF, which are critical in assessing trends and in clinical trial designs.<sup>1</sup> The MMRC also has developed a patient database consisting of contact information from 165,000 patients and has launched a new initiative called the patient navigator program to identify and match patients with clinical trials.<sup>1</sup>

### **Venture Philanthropy and Clinical Trial Networks**

One of the critical de-risking mechanisms in terms of development time/costs that many of the nonprofit disease organizations offer is their extensive network of clinical trial sites and expert investigators, as well as information about the ongoing trials in their networks. This offers the ability to conduct multi-site trials with expediency, combined knowledge, and access to quality data from the ongoing trials. Such clinical trial networks also provide the ability to scale up quickly in Phase III studies and, in some cases, conduct Phase IV studies.<sup>1</sup> An important aspect about such a network is the nonprofit disease organizations' collaborative approach to trials, as they often offer centralized review of clinical trial protocols, are able to set common policies to protect patient safety, establish standardized research procedures, share expertise among top researchers, and provide network-wide staff training.<sup>1</sup>

CFF may be one of the leading organizations that, through its Therapeutics Development Network (TDN), offers access to its network of eighteen clinical research centers that specialize in conducting Phase I and II studies for treatment of CF.<sup>1</sup> TDN centralizes and standardizes CF research while providing access to clinical trials data and CF experts through a centralized coordinating center at the Children's Hospital in Seattle, Washington.<sup>1</sup> To enlarge its network, CFF invested \$3 million in 2007 in forty-five new research centers in twenty states nationwide to build an infrastructure to help with patient recruitment and to increase its clinical network.<sup>1</sup> As discussed previously, the MMRF also offers a network of fifteen academic centers that collaborate in conducting multi-site clinical trials.<sup>1</sup>

To increase efficiencies, productivity, and sustainability of conducting clinical trials in developing countries, MMV works with a network of international organizations such as the Malaria Clinical Trials Alliance (MCTA), Malaria Vaccine Initiative (MVI), and the INDEPTH Network.<sup>1</sup> MCTA facilitates site preparation for effective conduct of Good Clinical Practices-compliant trials for malaria vaccines and therapies, while supporting the long-term development and sustainability of clinical trial sites in nine countries across Africa (Mozambique, Tanzania, Malawi, Gabon, Nigeria, Ghana, The Gambia, Kenya, and Senegal).<sup>1</sup> MVV also works with the European & Developing Countries Clinical Trials Partnership (EDCTP) to facilitate Phase II and III clinical trials in HIV/AIDS, malaria, and tuberculosis in sub-Saharan Africa.<sup>1</sup>

### Assessment and Recommendation

To reverse the trend of declining productivity and innovation, and embrace the new technological and scientific advances that will allow for safer and more effective treatment of diseases through stratified medicine, industry stakeholders must be open to unique models that could de-risk current drug development processes and increase their combined probabilities of success. Through our discussion, we have identified new collaborative mechanisms with nonprofit disease organizations that can not only help bridge some of the funding gaps in early-stage discovery and development of new technologies, but more importantly, de-risk the clinical process in terms of time and costs.

<b>FOUNDATIONS “DE-RISKING” PROCESSES</b>					
<b>Foundation</b>	<b>Academic Research Networks</b>	<b>Clinical Centers Networks</b>	<b>Tissue Banks</b>	<b>Patient Registries</b>	<b>Project Management</b>
Cystic Fibrosis	X	X		X	
Multiple Myeloma	X	X	X	X	X
Myelin Repair	X		X		
Juvenile Diabetes	X	X			X

In the short term, these mechanisms offer a model for the biopharmaceutical industry in how they can better work with existing nonprofit organizations to capitalize on their offerings. The elements of such a model would include biopharmaceutical companies collaborating with other groups, such as nonprofit foundations, who could establish and manage the programmatic research of networks of academic and investigators from small biotechnology companies, patient registries, and expert clinical centers. In return, large biopharmaceutical companies would provide some funding and commitment to take over the late-stage development of “de-risked” clinical candidates to approval and marketing. There could be several innovative ways to reward the nonprofits for their contribution without violating their mission or 501(c)(3) status.

A critical success factor in stratified medicine is the discovery of the biomarker and/or diagnostic kit. Intellectual property rights can be a potential barrier when there is only one supplier of the diagnostic kit, particularly if that kit has not been approved by regulatory bodies. This presents challenges in reimbursement, as well as potential liability issues if such a kit is used to qualify patients for a drug, and the specificity and sensitivity of the diagnostic test have not been established. This liability exists for both tests of efficacy and susceptibility to side effects. There is, therefore, need to address this downstream issue of potential biomarkers that are discovered in the NIH and other Biomarker consortia.

In summary, this paper focuses on ways to address two of the issues—return on investment and probability of success—that are barriers to the adoption of stratified



medicine by large biopharmaceutical companies. The various activities of some foundations serve to identify the relevant patient subgroups and generate data to better qualify potential drug candidates. We call these “de-risking” activities, which not only fill gaps in funding, but improve the probability of success of the drug discovery and development effort. These diseases also are excellent examples where subgroups of patients might be discovered and stratified, and prospective health care—anticipation, prevention, intervention—as described by Dr. Ralph Snyderman, could be pursued on a more rational basis. Thus collaboration between large biopharmaceutical companies and disease foundations provides an interesting model within which several aspects of the development and implementation of prospective health care and stratified medicine might be assessed for technological and economic feasibility.

However, a broader challenge remains in the ability to scale these de-risking mechanisms to a larger set of disease sectors, and on the question of who will bear the cost of creating the necessary infrastructures. One possibility is the U.S. government; as such efforts would be consistent with both the FDA’s Critical Path Initiative and the NIH Road Map. We would argue that both the FDA and NIH, under these two initiatives, could encourage the collaborative model suggested in this paper, either by disease category, such as cancer, where there is a known familial or genetic predisposition for the disease. In addition, two areas need to be urgently evaluated or assessed: the barriers that present intellectual property rights pose to adoption of the collaborative model, and the financial value of the varying de-risking strategies that we have discussed. These are the questions we pose today in opening the discussion on how we can make a business case for the growth and adoption of stratified or personalized medicine in the near future.

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# Investing in Personalized Health Care Innovation

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## **Background and Purpose**

Over the last decade, a series of key research developments in the fields of genetics and medicine have enabled the possibility of tailoring treatments for patients based upon the molecular basis of disease and/or the individual's ability to respond to a specific treatment. This possibility has given rise to the emerging field of personalized medicine.

Personalized medicine represents a major leap in the evolution of healthcare because it enables care providers to deliver the right treatment to the right patient at the right time. This ability will not only lead to improved health outcomes and better qualities of life both during and after illness, but may also help lower costs through greater efficiency of treatment.

Much in the same way that it helped create the biotechnology industry through its investments in Genentech, the venture capital industry has played a critical role in driving the development of personalized medicine by helping to translate multiple breakthroughs in molecular medicine technology into marketable products. Venture-funded companies like Genomic Health, Inc., Monogram Biosciences and Adeza Biomedical Corp. have already made an impact on patient health. The next generation of companies is expanding into new therapeutic areas, some of which are utilizing novel technology platforms. Venture capital will likely remain the primary source of financing for young innovators in this space due to the extraordinary risk associated with investing in healthcare technologies.

Despite its enormous promise, personalized medicine faces a number of barriers at what has become a critical point in its development. Some of these stem from current regulatory policies and the uncertain reimbursement outlook for new technologies. Others have resulted from the recent turmoil in the capital markets. *For each of these variables, even minute fluctuations and adjustments can alter the risk profile for even the most promising technology.* Working in concert, they can price risk beyond levels acceptable even to venture capitalists – effectively stunting the development of emerging technologies and undercutting the incentive for future innovation.

Within these contexts, the purpose of this paper is to:

- Explain the role that venture capital plays in innovation across industries.
- Illustrate the general process of venture investing.
- Outline the challenges and risks specific to healthcare investing.
- Articulate venture capital’s vision for advancing personalized medicine within this context.
- Examine current and potential business models within personalized medicine.
- Discuss personalized medicine’s implications for healthcare delivery.
- Identify current barriers to the development of personalized medicine.

### **Venture Capital: A Key Force in Innovation**

The venture capital industry drives innovation by turning ideas and advances in basic science into marketable products and services that improve people’s lives. They do this by identifying the most promising advances and then guiding their commercial development with expertise and funding.

Typically, venture capital concentrates on funding innovations that threaten to replace – or render obsolete – established products and services in a given marketplace. Venture capitalists use their expertise to find such “disruptive” technologies and evaluate which ones have the most market potential. Only the most promising advances get funded, and the venture capitalist typically takes an active role in guiding further development.

In this sense, the venture capital industry creates and maintains a de facto research and development pipeline for a wide variety of technology and knowledge-based industries. This role has become critical in recent years, as many public companies have slashed R&D budgets as a way to ease the quarterly scramble to meet earnings estimates. In some cases, venture capital has created entirely new industries.

The early-stage risk associated with disruptive innovations often precludes financing from traditional sources such as banks and public equity. Without someone to step in and assume this risk, many promising advances would have no capital for further development. By providing funding and expert guidance during this critical period, venture capitalists ensure that the most promising technologies have the best chance of making it to market – where they can make the greatest possible impact on quality of life.

By driving innovation in these ways, venture capital investment has fueled the development of many high-tech industries in the United States. These include biotechnology, medical devices, network security, on-line retailing, RFID and Web-based services. In fact, venture capital has helped to build innovative powerhouse companies such as Genentech, Microsoft, Google, Apple, Starbucks, Staples, eBay and FedEx.

### **Venture Capital Funds and the Investment Process**

The first venture capital firms date back to the 1930s and 1940s.<sup>1</sup> Up through the 1970s, by which time venture capital had established itself as an industry and a profession, investors at these firms worked as “generalists” – investing in companies and ideas across various industries. The relatively small size of the industry permitted this lack of specialization. In 1980, for example, the National Venture Capital Association tracked only three sectors: life sciences, information technology and industrial/energy.

Beginning in the 1980s, the skill set required for venture investing grew along with the industry. Successful venture capitalists needed the industry experience and insight to determine which innovations offered the most promise, domain business expertise to advise entrepreneurs and technologists in building portfolio companies, and the experience to manage the multi-stage investment process for those companies. As a result, venture investors (and often their funds) began to concentrate their efforts on a few sectors in which the partners had the most experience and that offered the most opportunities to innovate – most commonly software, industrial/energy, biotechnology, medical devices and diagnostics, and media and entertainment. Today, an individual venture capitalist typically specializes in one or two related sectors -- e.g. biotechnology and medical devices.

### **The venture capital process**

Venture capital firms raise funds from investors – most commonly large institutions such as corporations, foundations and public entity pension plans, but also from individual investors. The partners in a venture firm also invest their own money in their funds. Venture fund managers are compensated through annual fees associated with managing fund investments, as well as a percentage (carried interest) of the profits derived from successful investments. The latter are offset by losses associated with unsuccessful investments.

Venture capitalists generate profits and losses from the funds they raise by making equity investments in a range of portfolio companies. The average timeframe for this process is typically seven to 10 years. Generally, venture capital is used to purchase an equity stake in a series of rounds of investments in each individual company. Because venture capitalists tend to make investments in young companies, those companies often do not have products or services to generate cash flow from operations. As a result, they are not sufficiently creditworthy to take on debt. For this reason, venture capital is known for taking the highest risk in the spectrum of stages (with the exception of the “angel” stage) in which capital can be invested in building and running companies. Venture investors do not typically loan funds to their portfolio companies unless it is provided on a short term basis and eventually gets converted into equity.

As is the case with most investing, venture funds require risk diversification—especially considering the fact that they invest in one of the highest-risk stages of investing and often must wait 10 years or longer to realize their returns. To mitigate this risk, some venture firms raise separate funds dedicated to specific industries, while others specialize by investing in a single industry with multiple segments that can contribute some risk diversification.

Most young companies raise capital in a series of investments. Venture investors can participate in some or all of these financings. Young companies need only small amounts of capital (relatively speaking) when starting out – perhaps to develop a “proof of principal” or to reach a benchmark demonstrating measurable progress with a product or service. This enables them to raise capital in a series of later stages, at which points they can achieve higher valuations than in earlier rounds and can sell less equity – i.e. experience less “dilution” from the price at which they sell/accept new capital. This also allows the venture investor to invest more capital in the company, but in a way that demonstrates a series of increasing valuations associated with favorable progress. More detail about this process can be found in Appendices A and B.

After purchasing equity in a portfolio company and nurturing it for many years, a venture capitalist generates a return for the investors in the fund by selling that equity. There are multiple ways to generate liquidity for these equity investments. Most commonly, the company sells equity in the public market – enabling the venture investor to sell all or some of its stock to public market investors – or the company is sold to another firm. In the latter case, the investors receive either stock or cash upon the sale of the investment, thus providing either immediate or eventual liquidity. Again, this typically happens between seven and 10 years after the initial investment.

### **Venture Capital Investing in Healthcare<sup>1</sup>**

Venture investors generally assume significant technology development risks; however, healthcare presents some unique and additional challenges. These largely relate to the added complexity of long product development timeframes (often associated with clinical trials), government regulation and significant capital requirements, as well as the complexity of reimbursement associated with the healthcare payor system. These factors add up to larger capital requirements on the part of venture capitalists (and other stakeholders) and an investment time horizon that stretches to 15 years or longer. All of these increase risk.

Despite these complexities and the additional patience required, the venture capital industry invested approximately \$9 billion, or 30 percent of its total, in companies in the biotechnology (including pharmaceuticals and research tools companies), medical devices and healthcare services (including healthcare information technology) sectors in 2007.

Healthcare investing by the venture capital community for many years has been concentrated in the three areas mentioned above. During this period, the degree of specialization required for successful investing in each has increased.<sup>1</sup> In large part, devices and biotechnology investments have been tied to new technological

developments and related venture expertise, while services have met the needs of evolving healthcare delivery with a different set of skills and experience. Approximately 98 percent of the venture capital invested in healthcare (as measured by aggregate invested capital and number of investments) has been devoted to biotechnology and medical devices.

### **Venture capital and biotechnology**

The venture capital industry played a critical role in creating the biotechnology industry during the 1970s and 1980s. During this period, researchers achieved a number of key advances in the fields of gene sequencing and expression technology, recombinant DNA technology and monoclonal antibody technology. (Not coincidentally, all of these provide the foundation for personalized medicine today.) At the time, however, there existed no process for translating these advances into commercial products. In these years, for example, when Cetus Corp. developed polymerase chain reaction (PCR) and Genentech began cloning insulin, established pharmaceutical companies simply weren't inclined to take the risks involved in funding these advances. In both cases, venture capital stepped in to provide funding and management – helping both companies to advance their product development and creating a modern blueprint for building successful companies from innovations in medical technologies. Venture capital played a similar role during this time with biotech pioneers Amgen, Chiron, Biogen Idec and Genetics Institute, LLC.

Today, business models for biotechnology companies developing biopharmaceutical products continue to rely upon significant capital from both the venture industry and the public market. The capital is needed to sustain long product development cycles required for research and clinical studies, as well as manufacturing and product launch. Estimates vary for the cost of individual therapeutic products due to amortization of product failure costs along with successes; nonetheless cumulative individual product expense estimates range from \$500 million to nearly \$1 billion.

More so than in other industries, the risks associated with the increased costs and extended timeframes in the biotechnology sector preclude traditional sources of financing in the early stages of development. At the industry level, venture capitalists step in to not only fill the funding gap during the early stages, but also vet companies' scientific platforms and assess their commercial viability. They also lend management expertise and strategic vision to the companies in which they choose to invest.

### **Venture Capital Facilitates a New Vision for Diagnostics and Personalized Patient Treatments**

As described earlier, an important role of the venture capitalist is to help facilitate change within an industry. In the healthcare industry, the venture capitalist acts as an advocate not only for the entrepreneur but also for the patient by helping to drive advances in patient care – as demonstrated by the commercialization of advances in DNA research into biologic drugs (described in the previous section) and other treatments. Thanks to continued research and investment, these advances have in turn spawned personalized

medicine, which uses these technologies to improve patient outcomes and potentially reduce costs in the long term.

### **Vision for transforming role and value of molecular diagnostics**

Historically, diagnostic products have provided incremental and supplemental information to physicians and patients in managing care largely because they have contributed additional *pieces* of information to assemble into an overall assessment of disease and treatment.

New molecular diagnostics (or, personalized medicine) have the ability to raise the importance and value of the information derived from testing. Newer technologies enable the collection of data and analyses at a scale that was not previously possible – providing new insights about patients and diseases that can inform patient care and treatment. Also, new-generation tests may provide critical information for patient management, which in some circumstances may be as or more important than the value of existing therapies.

### **Technologies contributing to personalized medicine progress**

The foundation of personalized medicine lies within our efforts to better understand the biology of disease at the genetic and protein levels. Three technologies at the center of this effort are gene sequencing, gene expression and proteomics. Gene sequencing, made possible initially by Cetus' development of PCR, enables researchers to clone DNA and thus amplify genetic material. Gene expression technology allows researchers to identify genes in patients that indicate the presence of, or an increased susceptibility to, a given disease. In addition, it also helps illuminate the development and growth of cancerous tumors. Proteomics examines the molecular biology of diseases, enabling researchers to identify individual proteins associated with specific disease states and susceptibilities.

All of these technologies – either in development or application – have been informed and/or advanced by the Human Genome Project, which generated large quantities of genetic and genomic information and helped enable the acceleration of the sequencing process. Researchers have then studied this information in great deal to better understand the link of genetics to diseases; included in these efforts are large scale studies of both patients and agents of disease.

### **Personalized medicine: Understanding the patient and understanding the disease**

At the most basic level, personalized medicine has two goals: understanding the molecular nature of a disease and understanding how an individual will respond to therapy.

One of the best-known examples of the former is Herceptin<sup>®</sup>, a drug developed and marketed by Genentech, one of the first biotechnology companies to emerge from the venture industry. The recognition of the role of HER2 over-expression in breast cancer patients has aided in patient selection for treatment with Herceptin<sup>®</sup>. An important advance in understanding the patient's response to therapy is the ability to assess thiopurine (a group of chemotherapeutic agents) drug metabolism by measuring thiopurine methyltransferase (TPMT) activity in an individual patient. This advance has

enabled physicians to identify which cancer patients are likely to suffer adverse effects from the treatment. However, the opportunity to bring applications of more recent technological developments to bear in personalizing healthcare is driving venture capital investors to start new companies in this field today.

### **The business of personalized medicine**

Venture capitalists play a key role in building personalized medicine companies. They work with entrepreneurs to craft the business strategy, recruit the management team and often catalyze the key relationships necessary in building the business. While there is no formula for success, following a thoughtful process that addresses key issues increases the likelihood of success. Below are key early considerations in building a personalized medicine business:

- Clinical situation in which a physician needs more information to make an important treatment decision (for example, administer a life-saving therapy or device).
- Attractive target market from a business perspective; the ideal opportunity involves a large market coupled with a key clinical decision requiring a potentially expensive treatment (for example, placement of an implantable cardioverter-defibrillator (ICD) or administration of a biologic drug).
- Patient samples and technologies that can be used to address the clinical need. Often initial studies need to be performed to determine if together the samples and technology enable the development of the diagnostic.
- Management team with the appropriate scientific, clinical and regulatory expertise.

While the above factors may seem relatively straightforward, all components must come together to build a successful business. One factor of particular importance is the availability of well-annotated clinical samples, which makes development more practical. Such samples can reduce the risk of getting to clinical trials, the cost of development and the duration of development. Consider this example: Genomic Health's *Oncotype DX*<sup>®</sup> was developed using tissue archives that include data on each patient's five- or 10-year outcome. Had this archive not been available, development would have required new tissue samples and a waiting period of five to 10 years to track the clinical course of the patient.

### **Personalized medicine is reality: current products**

As described above, the goal of personalized healthcare or medicine is to tailor treatments for patients based upon their individual medication responses and the molecular basis of disease. This practice is evolving by addressing *groups* of patients that can be categorized by having similar susceptibilities and responses to therapy—in effect stratifying them by risk and response. While it is possible to envision a very broad range of future applications from these types of assessments, below are some examples of innovative personalized medicine companies funded by NVCA members. While the disease area may be different, these companies all have a common goal, providing answers to key clinical questions enabling better patient management.



- Early identification for individuals at risk for a disease. Genome scans identify genes which are associated with risk of disease, such as diabetes and osteoporosis. Currently, tests are available to consumers that identify these genes in individual carriers; two companies that market these tests are Navigenics and 23andMe. Understanding the genetic risk enables individuals to make lifestyle changes that may reduce that risk. Other tests detect patterns of markers in the blood that are early indications of potential disease. Tethys Bioscience has developed a test that quantifies the future risk of diabetes in patients who are at risk, but do not yet have clinical diabetes.
- Prognosis. Two recent examples of venture-backed companies with such products include XDX, which markets the non-invasive Allomap<sup>®</sup> test for heart transplant patient management to measure acute cellular rejection, and Genomic Health, Inc., which sells the Oncotype DX<sup>®</sup> test for breast cancer patients that assists in predicting the possible recurrence of disease in those with early-stage, invasive disease.
- Response to therapy. The recent introduction of the new Trophile<sup>™</sup> assay, by Monogram Biosciences, identifies which HIV patients are most likely to benefit from Selzentry<sup>™</sup>. Another company, ARCA Biopharma, Inc., has identified subpopulations of heart failure patients presumed to have greater therapeutic benefit from bucindolol, a new beta-blocker, based upon certain genetic subtypes. Individuals needing treatment for heart failure would be given a genetic test to see if they qualify for the new treatment. These types of applications are important – especially in those cases where a patient can be spared the significant side-effects of a given medication that actually offers a low likelihood of response. They are also very useful in rescuing otherwise failed drugs in clinical trials now and perhaps in the future, when safety problems arise.

Given that there is no shortage of clinical situations in which physicians could benefit from more information, many opportunities for the development of future products exist. The next generation of personalized medicine companies will continue to expand product offerings in oncology and cardiology, infectious disease and woman's health. Young companies are also tackling new frontiers, such as autoimmune disease, neurodegenerative disease and psychiatric disease.

### **Future business models**

Potential Model 1: Avoiding adverse effects. A future healthcare system could use electronic health records to identify patients with adverse effects, enroll patients (both with and without the adverse event) in research studies and screen for genes or biomarkers associated with the adverse event. This is currently not practical, nor is it likely to be in the very-near future – given that all patients would need to be tracked for all adverse events and all samples would have to be data-mined for genomic or proteomic correlations. However, today there is *no system at all* in place to call out the most likely targets for adverse effects research or to signal where or how payors will pay for cost-effective diagnostics that protect patients from prescriptions that will hurt them. Based on the risk and investment principles described so far, an optimal combination of public

investment could be balanced with rewards for specific product development in the private marketplace. A model example would be the basic research that took place in warfarin pharmacogenomics, which discovered several genes playing a key role in warfarin metabolism. A number of private companies are now competing to market increasingly rapid tests for these genes.

Potential Model 2: Safety alert or early intervention systems. Modern electronic health record technology could incorporate existing knowledge of adverse event reactions and drug/drug interactions in an “interactive health record” that incorporates patient specific information, data-based best practices, and laboratory test results in real time. This could provide optimal treatment pathways and ongoing appropriate tests to anticipate and reduce adverse events and to ensure the optimal treatment of the patient. One venture capital-based firm, Proventys, Inc., is currently developing important tools in this space. New business models will develop the best marketplace strategies for this category of personalized health technology, such as interfaces with pharma management systems, physician offices and payors. This space will be accelerated by policy initiatives such as adoption of ICD-10 disease codes, and electronic health records that facilitate rapid (ideally, immediate) transmittal of key information between the billing entities such as physician offices, hospitals and specialty laboratories. The Harvard Medical School/Partners Healthcare Center for Genetics and Genomics (HPCGG) has emphasized that the current relationships among these entities are many-to-many systems, making the information technology problems impossible to solve. The simplest solution, which does not exist today, would be a central data repository which can be accessed with appropriate confidentiality protections and permissions to result in the development of much more sophisticated solutions.

### **Personalized medicine and implications for the healthcare delivery system.**

As many of the preceding examples suggest, personalized medicine has the potential to transform the way care is delivered to patients across a full spectrum of conditions. To date, the healthcare system has caught only a small glimpse of the clinical and economic outcomes personalized medicine can yield. How soon these benefits can be fully realized depends on how quickly and effectively the healthcare industry can overcome the challenges inherent in harmonizing the interests of its multiple stakeholders. Clinicians, payors, manufacturers and health information technology firms alike will have to play meaningful roles in enabling innovations to fit into the context of the marketplace and achieve acceptance on a large scale.

The following provides a brief overview of challenges that key stakeholders face as the growth of personalized medicine accelerates in the coming years:

Clinicians: At the center of decision making. Through advances in personalized medicine, clinicians will be empowered to more precisely diagnose a patient’s condition and select the safest and most efficacious treatment based upon the patient’s unique clinical profile. However, the adoption of new technologies will pose a considerable challenge in the context of today’s busy medical practice. Among the challenges are (i) keeping pace with the proliferation of personalized medicine technologies (and the vendors providing them); (ii) identifying which patients are appropriate for the various

technologies being introduced to the market; (iii) interpreting molecular diagnostic test results in the broader clinical context for their patients; (iv) processing the sheer volume and complexity of data to make personalized clinical decisions; (v) reviewing and understanding the scientific evidence supporting the new technologies prior to relying upon them in routine practice; (vi) understanding the various payor coverage determinations to ensure appropriate reimbursement; and (vii) implementing the necessary operational processes for handling biological samples and working with various personalized medicine vendors.

Payors: Driving value-based approaches. As current medical management strategies such as disease management mature, payors are seeking innovative solutions to help reduce variability in care and control the rise of medical costs. It is in the best interest of payors to support personalized approaches to care where better understanding of patients' individual profiles (including their risks of an adverse event or potential response to a given therapeutic path) will guide better clinical decisions. Payors can play an important role in shaping the emerging market for personalized medicine by (i) identifying the clinical areas of greatest unmet need through population-level medical claims data analysis; (ii) setting clear requirements for the technology validation necessary to secure reimbursement coverage; and (iii) supporting the appropriate utilization of emerging technologies through the implementation of novel, value-based reimbursement models.

Diagnostic and biopharmaceutical manufacturers: innovators and educators. Personalized medicine represents a significant paradigm shift for both the diagnostics and biopharmaceutical industries. Biopharmaceutical manufacturers must reassess the fundamentals of their business as they contemplate the attendant shift from discovering the next blockbuster drug to unlocking the enormous value of targeted therapeutics that serve more distinct and segmented populations of patients. Diagnostic manufacturers must effectively demonstrate the increased value of their technologies as they play a more central role in the personalization of care. These manufacturers will help accelerate the acceptance of their own innovations by (i) effectively validating their technologies to support both payor reimbursement and clinical adoption; (ii) educating clinicians in novel ways with sound scientific support to ensure the appropriate utilization of these new technologies; and (iii) investing in the ongoing innovation necessary to establish a sustainable personalized medicine market.

Health information technology (HIT) vendors: Vital enablers. For personalized medicine to evolve from the current discrete instances of esoteric testing and targeted therapeutics to a more sustainable and widely accepted approach to care, a foundational system of information technology is required. HIT vendors have a unique opportunity to provide the dynamic, point-of-care decision support necessary to support the broad adoption of personalized medicine. These vendors must (i) develop more robust information solutions focused on delivering high-value decision support that empowers clinicians; (ii) make data more accessible and actionable to the care team within their current workflow; (iii) establish effective approaches to health information exchange to allow for a comprehensive view of a patient's medical history; and (iv) work with clinical data in novel ways to spur innovation while ensuring patient privacy and data security.

### **Barriers to Personalized Medicine Innovation**

In prior sections, this paper illustrates the considerable extent to which innovation relies on the ability of entrepreneurs and technologists to develop products from advances in research and commercialize these products. This section focuses on the complexity of this task in the field of personalized medicine and the barriers to success that currently exist.

As described earlier, some of these barriers exist inherently in healthcare investing. The longer time horizon and increased capital commitments necessitated by complex product development and clinical trials provide two such barriers. Market-driven fluctuations in the availability of capital provide a third. While these economic barriers are simply part and parcel of the process, a number of policy issues –specifically with regard to regulation and reimbursement – also hinder the development of personalized medicine. *These barriers are formidable and urgent, yet also within the government and the industry's power to mitigate – if the two groups work together now to remove them.*

### **Laboratory medicine deals with a complex transaction system**

Successful company development in personalized medicine involves simultaneously balancing:

- Extremely sophisticated technologies, such as gene chip microarrays.
- The complex nature of medical knowledge (clinical trial environment; human subjects regulations; the need for evidence-based medicine).
- The complex decision-maker marketplace (e.g. physicians; standards of practice; society guidelines; accepting innovation versus the tried-and-true in medical technology).
- The complex payor marketplace (coverage decisions by insurers as well as the underlying coding/reimbursement system).

A laboratory medicine test faces this transaction system:

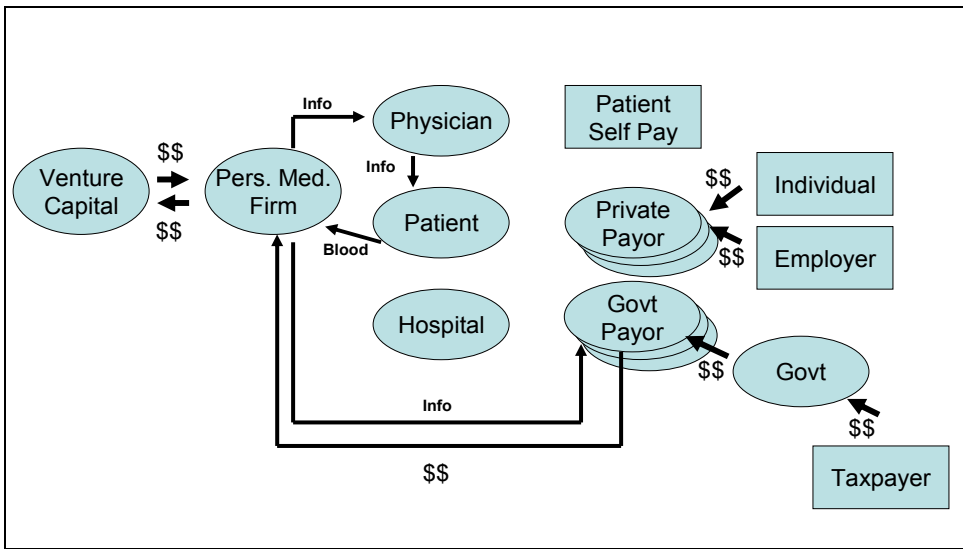


Figure 1

Figure 1 shows arrows for just one payment pathway (in this case, a government payor). Other arrows would connect different payors to the laboratory. Note that the personalized medicine lab ultimately receives money originating from one of four sources (represented by rectangles): patient self-pay, from taxpayers via a government payor, or from an individual or an employer via private insurance.

The diagram risks understating the complexity of the information transactions involved.<sup>1</sup> A national lab – even a one-test startup lab – must deal with hundreds of private and government payors. Each payor must make coverage and pricing decisions (which can involve complex technology assessments) about the test and each payor (at least in principle) needs to know something about the patient’s condition at the time of the test.

The arcane complexities of the insurer coding and pricing systems for laboratory tests have been well-documented.<sup>1</sup> During the early investment stages, the venture capital firm must project five to 10 years in the future how physicians, patients, hospitals, private payors, government payors and the self-pay patients will respond to the test, as well as the test’s likely position in the marketplace relative to both existing alternatives and alternatives likely to be introduced in coming years. All of these factors must be tracked during, or informed by, optimally planned and staged investments which lead to the most efficient reduction in risk as the project develops and investments increase. (As shown earlier, with the reduction in risk, the projected value of the company increases substantially, which in turn makes a new investment round possible.)

Venture capital investors must evaluate the likely stances of third-party payors closely – a necessity that is very specific to the medical technologies sector. Generally, payors are concerned about two issues: 1) the overutilization of diagnostic tests and treatments and 2) the absolute costs of these tests. Thus, the challenges for venture capitalists regarding this new generation of molecular diagnostic tests stem from the fact that the development process is costly, as like therapeutics, they often involve the productization of new

technologies and large clinical trials. These factors in turn drive up prices for patients and payors.

However, entrepreneurs and developers of these technologies are willing to risk the concerns of payors because the results generated by them provide information of much higher value for patient care. Therefore, despite the initial higher cost, these diagnostic tests will ultimately lead to more cost-effective patient management for payors.

### **Specific reimbursement considerations**

As discussed previously, the current products that are most strongly associated with personalized health care are molecular diagnostics. Today, far more is known about the molecular heterogeneity of major diseases, including cancer, than was known even 10 years ago. Research has made it clear that targeted and more effective medical treatments will often be unattainable unless physicians have precise molecular information about each patient's disease. That is, there will be no "magic bullet" chemotherapy for "colon cancer" across all patients, but there may be a very effective treatment for those patients whose colon cancer expresses Gene X.

In many ways, these tests seem to be the easiest to integrate into the existing care delivery system. If Chemotherapy Drug X is effective when tumors express Gene X, then we can test those patients and prescribe the right drug to the right patient at the right time.

Although the integration of these tests into clinical care would seem like a fairly straightforward process, companies and investors have found two key factors providing barriers to innovation. These are 1) level of evidence for payor coverage and 2) legacy pricing systems.

Diagnostic tests: level of evidence for payor coverage. Payors are most experienced at performing technology assessments for drugs and for other therapeutic interventions (e.g. ultrasound for kidney stones.) Diagnostic tests present several difficulties for payors. First, few payor guidelines for technology assessment contain the same level of sophistication and granularity as the research that led to and supports the technology being assessed.<sup>1</sup> Some guidelines don't even recognize the difference between diagnostic and therapeutic applications. Second, there are few guidelines on the degree to which clinical benefit can be extrapolated from test accuracy or retrospective studies, or whose extrapolation is credible and why. For example, imagine a researcher studies Gene X in an archive representing 100 colon cancer patients treated with drug XYZ. Only the 20 with Gene X responded, and responded well; the other 80 did not respond at all and quickly died. Should a randomized trial be conducted, where 80 percent of entrants will be treated with XYZ despite having Gene X? Can we assume Test X is necessary and impacts clinical care greatly? What if the numbers were less clear cut? The lack of consensus guidance leaves both innovators and payors with a great deal of uncertainty in how to evaluate diagnostic tests for coverage.

Diagnostic tests: reimbursement. Most traditional diagnostic tests long ago became commodities (such as a serum glucose test or a thyroid hormone test). Most payors pay

fixed and inexpensive test prices related to Medicare’s laboratory fee schedule, which was established in 1984. Since then, many stakeholders have asserted that the reimbursement environment for novel diagnostics is much more challenging than the environment for other medical devices or drugs.<sup>1</sup> In the U.S. payor system, new drugs are assigned specific codes for insurance claims and paid at market prices that are set relative to alternative drugs. The payor system for diagnostic tests has developed in a different and less consistent manner. Diagnostic tests are usually described by generic codes (e.g. microbiology antibody test) and paid at a fixed rate (say, \$30). In the case of one novel molecular medicine test (the *Oncotype DX*<sup>®</sup> test), however, private insurers and Medicare have paid near list price – several thousand dollars in this case – for the test. High levels of uncertainty regarding “value-based pricing” of molecular diagnostics pose serious difficulties in the venture capital investment model because such uncertainty inverts the assumption of *progressive* risk reduction (the notion that a venture becomes less risky as it matures) outlined in prior sections. For example, in the case of a novel molecular test, the uncertainty over how Medicare will price it resides at the *far end* of the development and investment pathway; this uncertainty remains constant during progressively larger staged investments. Prices that converge on marginal costs are characteristic of mature and highly competitive markets, but make innovation impossible.<sup>1</sup>

Changes, such as published guidance, which make coverage and reimbursement more predictable will reduce the overall level of risk for innovators and thus encourage innovation in ways that are otherwise costless to the system.

### **Specific diagnostic oversight issues**

New molecular diagnostic tests primarily fall into classes of products defined by the Food and Drug Administration (FDA) as in vitro diagnostic (IVD) tests or in vitro diagnostic multivariate index assays (IVDMIA). The former are often less complex than the latter, though precise regulatory definitions are still being actively reviewed as new products reach laboratories and the FDA.

Historically, oversight responsibility for in vitro diagnostic products has resided in both the FDA and the Center for Medicare and Medicaid Services (CMS). FDA approves the safety, efficacy and manufacture of IVDs under its authority to regulate medical devices, while CMS oversees compliance with performance standards for laboratories under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). For many years, the FDA has exercised “enforcement discretion” for emerging diagnostic tests largely performed by specialized laboratories. However, in July 2007, the FDA published its most recent guidance on the topic, signaling the agency’s intent to actively review all current and new IVDMIA that have not already been voluntarily submitted for review. This guidance has sparked significant dialogue within different industry groups, as well as between industry and the FDA.

The FDA’s regulation of IVDMIA will follow the device evaluation path--where substantial equivalence to an existing, or “predicate”, device is established for the new test, or a more extensive, pre-market approval (PMA) path may be required. A number of new molecular diagnostic tests have been developed as Laboratory Developed Tests

(LDTs, or “home brew” tests) for exclusive use in CLIA-certified laboratories and have not been reviewed by the FDA. The July IVDMIA guidance, when implemented, will require these tests and others under development to undergo more extensive regulatory evaluation, in some cases requiring clinical data that may or may not have been developed prior to their use as LDTs.

There are number of outstanding issues associated with new IVDMIA development and the FDA’s plans to actively review this class of tests. The outcome of this review could significantly influence innovation by the venture community. These include, but are not limited to:

- Developing a clearer understanding of what constitutes an IVDMIA (i.e. the definition).
- Identifying what types of data will be required for favorable claims reviews (i.e. retrospective versus prospective clinical trials).
- Understanding the evaluation process for new algorithms integrated into test design and analysis.
- Clarifying the roles for CMS and the FDA in dual regulation of this class of devices.
- Providing a reasonable transition time for tests currently marketed as LDTs, as well as those under development.

As is the case with many new technologies, patient safety concerns must be balanced with regulatory processes. This must be done without defeating innovation, however.

This discussion has been devoted to the oversight of new molecular diagnostic tests largely for two reasons. First, the vast majority of venture-backed companies that are focused on personalizing healthcare are developing these types of products. Second, the issue is timely for the venture community as it weighs ongoing investment in companies developing new tests. However, regulatory decisions are also evolving for pharmaceutical product development--ones that anticipate incorporating new molecular technologies. For example, the FDA is discussing plans to require the collection of DNA samples from all patients participating in clinical trials, so that such material can be accessed in the future if drug-related safety issues arise. Further guidance from the FDA would also be constructive in updating the preliminary regulatory path for co-developed diagnostic and therapeutic products.

### **Conclusion**

Thanks to continued federal funding and the extraordinary promise for improving health outcomes, advances in the fields that drive personalized medicine will continue. Demand for treatments and therapies based on these advances will also grow as people begin to understand aspects of their personal health in unprecedented detail and look to take greater control over that health. Given these realities, the question becomes: Will the industry be able to meet this demand by bringing advances in personalized medicine to the marketplace?



The fundamental process for bringing innovations in this sector to market probably won't change. Federal and academic research will continue to move the science of personalized medicine forward. Innovation will continue to spring from small companies – as opposed to large institutions and corporations – because of the freedom and creativity they encourage. Venture capital will continue to step in during the critical early and middle stages to assume the risks inherent in building these companies.

Unfortunately, venture capital can only take personalized medicine and the innovative companies that drive it so far before the acute regulatory and reimbursement barriers discussed in the previous section begin to hinder development. The consequences of this inefficiency are significant – given personalized medicine's potential for dramatically improving both the efficacy and efficiency of healthcare delivery. *Together, these elements could play a major role in broader healthcare reform in the U.S. by reducing costs and enabling greater individual participation in health outcomes.* Without a joint effort by government and industry players to remove or ease existing barriers, however, personalized medicine may never achieve its full potential.

## **APPENDIX A**

### **Guide to venture capital investing rounds and terminology**

Most young companies raise money in discrete stages. This practice enables the owners and their venture investors to raise funds at increasingly higher levels of valuation as the company's assets grow and its risk profile improves. (See Appendix B for step-by-step details.)

The earliest round of financing is typically called either a “seed”, “first”, or “Series A” (denotes the legal name for the category of stock and investor) round. In most cases, it represents the first time that a company raises funds and usually garners a small amount of capital (i.e. between one and several million dollars) from only one or a couple of investors. Funds raised during this round may contribute to product development and market research. Other uses include building a management team and developing a business plan if the initial steps are successful. This is a pre-marketing stage.

Subsequent rounds are called “follow-on” rounds – typically named “Series B, C, D” and so on. These rounds generally draw down larger amounts of capital from an increasing number of investors as the company's needs grow. Series B capital often funds additional product development, product launch and initial marketing efforts. Once a company is producing and shipping its product and has growing accounts receivables and inventories, Series C capital may provide funds for an initial expansion. Beyond this point, the company may engage in additional rounds, or even begin to take on some debt and possibly sell equity to public market investors. Such late stage rounds are commonly called “mezzanine” rounds.

While many venture funds invest in both the early and follow-on rounds, some also specialize in the stage at which it makes its investments. For example, the unusual expertise and operational experience required for creating companies from scratch have

given rise to funds specializing in seed round investment. Similarly, mezzanine rounds often call for funds that focus on taking companies public and/or selling them to other companies. Such funds are commonly affiliated with public market investor funds. Other funds, known as “crossover” funds, may specialize in investing in both the late private rounds of investment as well as the public market (although most venture funds in the healthcare space reserve the ability to make investments in their portfolio companies in both private and public rounds of investment).

## **APPENDIX B**

### **Venture financing:**

#### **How portfolio companies generate and preserve equity through multiple financing rounds**

The venture capital financing process begins when venture capital investors and the founding entrepreneur(s) of Company A negotiate a valuation that takes into account the company’s technology, experience and other assets, as well as the risks it entails. At the first stage of financing, the company has a much higher risk of failure than success and will require significant additional capital to develop its products. In this example, Company A has been valued at \$10 million (most start-ups are valued below this amount, but it is a useful number for demonstration purposes).

Next, the founders of Company A raise capital by selling 40 percent of the company’s equity to “first round”, or Series A investors (i.e. venture capitalists). The company now holds \$4 million in cash, with 40 percent of the firm’s equity held by venture capitalists and 60 percent owned by founders and employees.

Assume that Company A is successful in further product development and that the likelihood of success gradually increases (along with a commensurate reduction in risk of failure). In Year Three, the company demonstrates measurable progress and seeks additional capital at a “higher valuation”. For this second round (or Series B), the owners find new investors who believe that the pace of product development, competitive advantages and markets sizes for planned products, discounting new risk and return analyses for timing of liquidity and return on investment, value the company at \$50 million. In this case, the 40 percent purchased earlier by Series A investors is now worth \$20 million. One-half of the remaining \$30 million of founder and employee value is sold to the Series B investors for \$15 million. At this point the series A investors continue to own 40 percent of the company, the Series B investors own 30 percent of the company ( $1/2 \times 60$  percent), and the original founders and employees own 30 percent of the company (100 percent - 40 percent - 30 percent). The company has \$15 million in new capital and has invested the original \$4 million in product development.

At this time, typically, 70 percent of the board members will be represented by outside investors. They will look for the optimal exit strategy, such as taking the company public or selling to a larger firm. But in this example, at Series B, the company still has a limited chance of success and a reasonable chance that it will fail – in which scenario the \$19 million that was raised will be lost.



# Patients' and Consumers' Interests and Perspectives in Personalized Healthcare

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## I. INTRODUCTION

***“Progress in [personalized medicine] will characterize medicine in the 21st century and extend life span much like the use of antibiotics did in the 20th century.”***

-- Gerald Levey<sup>1</sup>, Provost and Dean, University of California, Los Angeles School of Medicine, *FasterCures* Board member

The 20<sup>th</sup> century witnessed the greatest expansion of life expectancy in the history of humankind. The challenge for the 21<sup>st</sup> century is to not only extend the length, but to also improve the quality of life by preventing and defeating deadly and debilitating diseases. Across the spectrum - from basic science to clinical research to health services research - the impressive advances of recent decades in the biomedical, physical, computational, and behavioral and social sciences present unprecedented opportunities to improve human health and quality of life. Capitalizing on this reality will usher in an era of personalized medicine and solidify its place at the frontier of medical science.

The ultimate value of personalized medicine will be to improve treatment options for patients and prevent the onset of disease in the first place. But to realize these important gains, we need to transform our current research and healthcare systems from the outdated model of the last century to an integrated, information-based, high-quality, health-sustaining model that will extend life expectancy and improve the quality of life for generations to come.

***To achieve this transformation the new system must focus on patients. How personal is personalized healthcare and what do consumers think about the advent of this era?***

Embedded within each patient is the information – family history, medical records, lifestyle, biological samples, etc. – that is crucial to understanding, treating, and

<sup>1</sup> Levey G, “Personalized Genetic Medicine: In Theory and In Practice,” **FasterCures** Essays for Change, <http://www.fastercures.org/voice/essays>.

preventing disease. Patients need to be empowered by accurate information and armed with a clear understanding of the opportunities to:

- participate in research and clinical trials;
- donate biological material such as tissue and blood samples; and
- advocate to have interoperable electronic health records (EHRs) to aid care and research.

As a contribution to U.S. Department of Health and Human Services Secretary Michael O. Leavitt's Personalized Healthcare Initiative, *FasterCures* submits this white paper summarizing the perspective of patients and consumers, the prime constituency in the discovery of personalized medicine advances and the ultimate beneficiaries.

To paint a complete picture and accurately represent the numerous patient perspectives on personalized healthcare, *FasterCures* conducted a qualitative research survey of disease research organizations, patient advocates, and patients to gauge understanding, awareness, and expectations of personalized healthcare and elucidate the issues that affect millions of Americans.

## II. The Path to Personalized Medicine: Patient Involvement

***“Success is when everyone can learn which methods and treatments work, and which don’t, in days instead of decades.”***

-- Carol Diamond and Clay Shirky<sup>2</sup>

In 1799, explorers unearthed in Egypt a stone slab – the Rosetta Stone – bearing parallel inscriptions in Greek, Egyptian hieroglyphic, and demotic characters, which made it possible to decipher the written language of the ancient Egyptians and the stories that it told about the people and their culture. Each of us is, in a sense, a Rosetta Stone, for within us is the information necessary to unlock the relationship of genetics, proteomics, behavior, nutrition, and environment to the emergence and, ultimately, the management of disease.

The three "languages" of our Rosetta Stone are medical records; biological material such as tissue, blood, and DNA; and our biology as observed in clinical research. By participating in clinical research – trials to test potential new therapies as well as epidemiological, observational, or natural history studies – and by providing tissue samples, blood, or medical histories, patients can provide critical information and resources, without which the search for cures and advancements in personalized medicine could slow to a halt.

**Many respondents to our survey felt that the greatest payoff to personalized healthcare will come from leveraging the patient’s role in these critical areas:**

<sup>2</sup> Diamond C, Shirky C, “Health Information Technology: A Few Years of Magical Thinking?” Health Affairs, September/October 2008; 27(5): w383-w390.

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- **Biological specimens.** It is important that patients understand the key role that biospecimens play in medical research, and how critical they are to future research discoveries. To understand the connections between genes, proteins, and the environment, sophisticated comparisons must be conducted. These comparisons cannot be done by hand or by eye, or patient by patient.

It is interesting to note that the importance of tissue sample collection was generally not mentioned by our survey respondents. Some pointed out that patients can be uncomfortable with the notion of donating their tissue, and the time to educate patients about tissue donations for research is not at the moment a consent form is being signed for diagnosis or clinical care. Patients and patient groups must be brought into the process as partners in helping to ensure that the patient community understands how biobanks work, and the role they play in the clinical research infrastructure. *FasterCures* has a website devoted to this topic [www.biobankcentral.org](http://www.biobankcentral.org).

- **Clinical trials.** Clinical trials are the only way of evaluating whether new diagnostics, drugs, experimental medical devices, and surgical techniques actually work. These trials are dependent upon patient involvement. The *FasterCures* Patients Helping Doctors (PHD) Program facilitates the understanding of the critical role patients play in research, with the ultimate goal of increasing patient participation in this process. We have found that there are many reasons for the lack of patient participation including:
  - patients not having enough information about clinical research,
  - physicians not having enough information and not informing their patients about the possibility of enrolling in a clinical trial, and
  - patients and doctors having misconceptions about clinical trials.<sup>3</sup>

Respondents to our survey outlined how highly motivated their patients are to participate in clinical trials. For example, in the National Institutes of Health (NIH)-sponsored Alzheimer’s Disease Neuroimaging Initiative (ADNI) trial, the enrollment has exceeded the study program director’s expectations despite some of the painful medical procedures trial participants are undergoing.<sup>4</sup>

Overall, patients who enter trials see it as part of their larger role of advancing science. One respondent said, “Within the cancer community, there is a profound altruistic feeling. They want to help by participating in trials, and the data shows that when they do, they feel positively about the experience.” Survey respondents did feel

<sup>3</sup> See the *FasterCures*’ white paper, *Clinical Trials Recruitment and Retention: Best Practices and Promising Approaches*, September 2006, [http://www.fastercures.org/objects/pdfs/meetings/FC\\_ClinicalTrials\\_report\\_art\\_spg.pdf](http://www.fastercures.org/objects/pdfs/meetings/FC_ClinicalTrials_report_art_spg.pdf).

<sup>4</sup> Laurie Ryan, Program Director, Alzheimer’s Disease Clinical Trials, National Institute on Aging, NIH, Presentation Comments, Institute of Medicine Forum on Drug Discovery, Development, and Translation workshop “Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies,” June 23, 2008, Washington, DC.

we need to incentivize more participation in clinical trials; otherwise, it will be hard to move personalized medicine forward.

- ***Electronic Health Records (EHRs).*** The promise for personalized medicine offered by integrated EHRs is immense. EHRs will go a long way to solving the information gap that often exists as patients travel from one provider’s office to another. EHRs will also provide much-needed ways to aggregate data about treatment and outcomes for research and offer unprecedented opportunities to speed up the quest for cures. As patients wait for better therapies and eventual cures however, EHRs will help to manage some of the chaos created by complex individual co-morbid conditions.

Enabling research use of information collected in the patient care process could significantly accelerate medical research. EHRs and clinical databases and warehouses can make the work of specialists in one discipline widely accessible to specialists in many disciplines. EHR systems could speed data acquisition and searching, allow mass computing and sampling, and provide the research community access to a broader and more diverse patient population. Improvements made in EHR systems in response to research needs will ultimately serve clinical care needs as well.

### III. The Personalized Medicine Landscape: What Do Patients and Consumers Think?

***“We must remember that the true foundation of this progress is public trust. It is not enough merely to develop the knowledge and information that will make personalized healthcare possible. In addition to developing the information, we must use it correctly.”***

-- Michael O. Leavitt, Secretary of U.S. Department of Health and Human Services<sup>5</sup>

It would be inaccurate to say there is only *one* patient community. There are hundreds, perhaps thousands of them, each defined by different experiences as their members manage disease from diagnosis through treatment and possibly cure. Patient awareness and understanding of personalized medicine and healthcare has begun, but it will be an ongoing process that will vary and evolve based on the disease.

**The national discussion about personalized medicine has mostly occurred at the 30,000 foot level and has yet to comprehensively engage and permeate the broad array of patient communities with its myriad concerns.**

#### ***Methodology***

In order to understand the key role of patients in driving the adoption of personalized healthcare approaches, *FasterCures* conducted a qualitative research survey of disease research organizations, patient advocates, and patients to determine understanding, awareness, and expectations of personalized healthcare. For the survey, we reached out to senior executives of 10 groups in the *FasterCures* Redstone Acceleration & Innovation

<sup>5</sup> See the Department of Health and Human Services report, Personalized Health Care: Opportunities, Pathways, Resources, September 2007, [www.dhhs.gov/myhealthcare/news/phc-report.pdf](http://www.dhhs.gov/myhealthcare/news/phc-report.pdf).

Network (TRAIN). We also identified an additional five national organizations that are not in TRAIN that represent the issues related to diseases that affect millions of Americans.

TRAIN is a group of unique nonprofit foundations that fund medical research across a spectrum of diseases, from breast cancer to Parkinson’s disease.<sup>6</sup> In many cases TRAIN’s member foundations have been created by patients and their families who are frustrated by the slow pace of change in the traditional medical research system. They represent the kind of organizations that are fast becoming the engine behind innovation in disease research – collaborative, mission-driven, strategic in their allocation of resources, and results-oriented. They are organizations that have a singular focus on, and a significant stake in, getting promising therapies from the laboratory bench to the patient’s bedside as rapidly as possible.

**Figure 1 – FasterCures’ TRAIN Program**



TRAIN has come together under the auspices of *FasterCures* – a nonprofit “action tank” whose mission is to save lives by saving time in the research, discovery and development of new medical solutions for deadly and debilitating diseases. The TRAIN network helps its members to more easily and effectively support each other’s efforts to produce better and faster results, and to bring their sense of the urgency about conducting more and better bench-to-bedside translational research to the medical research community as well as to the public at large.

<sup>6</sup> See [www.fastercures.org](http://www.fastercures.org) for more information on FasterCures’ TRAIN program.



*FasterCures* surveyed groups using email and telephone-based methods and attempted to reach representatives from a variety of diseases ranging from preventable to incurable. Specifically, representatives from the following groups were interviewed:

<b>Organization</b>	<b>Organization Overview</b>	<b>Contact, Title/Role</b>	<b>Outreach Mechanism</b>
Accelerated Cure Project for Multiple Sclerosis	Organizes the research process for multiple sclerosis and encourages collaboration between research organizations and clinicians.	Art Mellor, President & CEO, Co-Founder, Director	E-mail Correspondence
Alpha-1 Foundation	Identifies those affected by Alpha-1 Antitrypsin Deficiency (Alpha-1) and improves the quality of their lives through support, education, advocacy, and to encourage participation in research. The Association has over 70 volunteer-led support groups around the U.S	John Walsh, President	Phone Interview
Alzheimer's Association	Mission is to eliminate Alzheimer's disease through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health. The organization's achievements and progress in the field have given thousands of people a better quality of life and brought hope for millions more.	Jennifer Zeitzer, Associate Director, Federal Policy	Phone Interview
American Heart Association	Nation's oldest and largest voluntary health organization dedicated to building healthier lives, free of heart disease and stroke. In fiscal year 2006-07 the association invested more than \$554 million in research, professional and public education, advocacy and community service programs to help all Americans live longer, healthier lives.	Derek Scholes, Government Relations Manager	Phone Interview
Autism Speaks	Focuses on increasing awareness of autism spectrum disorders, to funding research into the causes, prevention, treatments and cure for autism, and to advocating for the needs of affected families.	Nancy Jones, Program Director	Phone Interview
COPD Foundation	Mission is to develop and support programs which improve the quality of life through research, education, early diagnosis, and enhanced therapy for persons whose lives are impacted by Chronic Obstructive Pulmonary Disease.	John Walsh, President	Phone Interview
Epilepsy Therapy Development Project	Mission is to advance new therapies for people living with epilepsy; supports the commercialization of new therapies through direct grants and investments in promising academic and commercial projects.	Joyce Cramer, President	Phone Interview
Friends of Cancer Research	Raises awareness and provides public education on cancer research in order to accelerate the nation's progress toward better tools for the prevention, detection, and treatment of all cancers.	Jeff Allen, Executive Director	Phone Interview
Hydrocephalus Association	Provides support, education and advocacy for people whose lives have been touched by hydrocephalus and the professionals who work with them; advocates for increased research and funding to advance understanding, improve diagnosis and treatment, and find a cure.	Dory Kranz, Executive Director	E-mail Correspondence
Lance Armstrong Foundation	Focuses on cancer prevention, access to screening and care, research and quality of life for cancer survivors. LAF has raised more than \$260 million for the fight against cancer.	Adam Michael Clark, Director of Health Policy	Phone Interview

Michael J. Fox Foundation for Parkinson's Research	Mission is to ensure the development of a cure for Parkinson's disease within the decade through an aggressively funded research agenda. The Foundation has funded over \$126 million in research to date.	Debi Brooks, Co-Founder	Phone Interview
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National Health Council	Represents 119 national health-related organizations working to bring quality health care to all people. Its core membership includes some 50 of the nation's leading voluntary health agencies representing about 100 million people with chronic diseases and/or disabilities. Other Council members include professional and membership associations, nonprofit organizations with an interest in health, and major pharmaceutical and biotechnology companies.	Myrl Weinberg, President	Phone Interview
Parkinson's Action Network	Serves as the voice of Parkinson's on numerous public policy issues affecting the Parkinson's community.	Mary McGuire Richards, Deputy Chief Executive Officer	Phone Interview
Prostate Cancer Foundation	Provides funding for more than 1,400 research projects at nearly 150 institutions worldwide; advocates for greater awareness of prostate cancer and more government resources, resulting in a twenty-fold increase in government funding for prostate cancer.	Jonathan W. Simons, President & CEO	Phone Interview
Susan G. Komen for the Cure	Largest grassroots network of breast cancer survivors and activists fighting to save lives, empower people, ensure quality care for all and energize science to find the cures. Invested more than \$1 billion in the fight against breast cancer in the world.	Elizabeth Thompson, Managing Director, Public and Medical Affairs	Phone Interview

Additionally, *FasterCures* posted a description of the goals of this white paper along with several questions on *PatientsLikeMe*<sup>7</sup> to solicit candid feedback from patients. We received responses from 32 patients. The responses we garnered from this process are woven throughout this white paper. More patients are turning turn to online tools like *PatientsLikeMe* where they interact to help improve their outcomes. The data they provide helps researchers learn how these diseases act in the real world.

### ***Overall Perspectives About Personalized Healthcare***

Respondents identified a wide spectrum of current applications of personalized medicine for specific diseases. Our survey found that patient awareness and understanding of personalized medicine has begun, but it will be an ongoing process and that educational process will vary based on the disease. Everyone interviewed had some understanding of what personalized healthcare was, and the potential benefits it will offer as we transition from a trial-and-error, one-size-fits all approach to treatment to one that is tailored to individuals. Respondents on *PatientsLikeMe* were aware of it in a general sense, but didn't necessarily know that it was called personalized healthcare.

There were some differences in whether people thought personalized healthcare was simply a way to understand the genetic and individual basis of disease or rather another way to segment patient populations and offer tailored therapies.

<sup>7</sup> PatientsLikeMe is the leading treatment, symptom and outcome sharing community for patients with life-changing conditions, and creates new knowledge by charting the real-world course of disease through the shared experiences of patients with ALS, Multiple Sclerosis, Parkinson's, HIV, and Mood conditions (including depression, bipolar, anxiety, OCD and PTSD). The company endeavors to create the largest repository of real-world disease information to help accelerate the discovery of new, more effective treatments. See [www.patientslikeme.com](http://www.patientslikeme.com).

Even among groups who characterize themselves as less engaged on this issue, there was still widespread acknowledgment that this is the direction in which 21<sup>st</sup> century medicine is heading. There was however, a sense that the leadership of the patient community lacked a clear sense of what was, and was not personalized medicine, identifying the need for additional work on definitions and illustrative examples. A wide spectrum of current applications of personalized medicine to specific diseases was represented by respondents including warfarin testing and BRAC1 for breast cancer.

### *Citing the Need for Patient-Centered Care*

Some of the issues raised by the interviews were not always specific to personalized healthcare but instead represented challenges that patients have faced for years. Specifically, respondents expressed widespread frustration with the inability of the healthcare system to address each patient's needs, and to efficiently and effectively coordinate care across providers and conditions. **Personalized healthcare will not be immune to these challenges, and as innovative treatments and diagnostics grow more complex, it is a reasonable concern that the insufficiencies within coordination of care will become exacerbated.**

The need for *patient-focused care* is increasingly more important as scientific discoveries bring us closer to personalized health care. "We need to address the medical and social goals of the whole person with multiple co-morbidities in the context of their individual life circumstances. We must try to get away from a purely medical model that offers only a disease-by-disease approach without consideration of personal desires such as living independently, remaining in the workforce or managing chronic pain," offered Myrl Weinberg, President of the National Health Council, which represents over 120 member organizations including patient advocacy organizations.

"People with chronic conditions will interact with the health sector for the rest of their lives. If patients are an afterthought and not engaged at the front end of the research process, our collective opportunity to address the complicated medical and social needs of the whole person may be lost, and the scientific advances of personalized medicine and the expected benefits will be diminished," said Weinberg.

Even more strongly, a patient said, "What I've experienced so far in most hospital environments is all but personalized... I felt more like cattle than a human being in general."

If patients are an afterthought and are not engaged at the front end of the research process, the scientific advances of personalized medicine and the expected benefits to patients will be hindered. If patients are to be involved in clinical research leading to advancements in personalized healthcare, they need better information and a deeper understanding of it based on clear, concise, and accessible information.

A theme emerging from our analysis was that perspectives on personalized healthcare are directly shaped by the state of the science in a given disease area. All groups expressed knowledge of personalized healthcare and a majority had participated at some level in

meetings and discussions on this topic. However, for diseases with a strong understanding of the mechanism causing the illness and associated targeted therapeutics, respondents offered an even more robust understanding and appreciation of personalized healthcare.

Many recognized the potential advances on the horizon for their disease area, but remarked that it still feels far enough away that it is difficult to reach and therefore difficult to plan for. “We are here and we are far away from personalized healthcare all at once,” mentioned one respondent. With some chronic diseases like heart disease it is difficult to project where the science will go, since its prevention and its treatment utilize both medical and public health approaches.

Co-morbidities are an increasing issue for many patient groups. For example, 65 percent of patients with chronic obstructive pulmonary disease (COPD) report six to ten co-morbidities, including conditions such as arthritis, diabetes, and cardiovascular disease.<sup>8</sup> For example, in the case of Alzheimer’s disease, 96 percent of patients have other conditions and data shows that Medicare spends up to three times more for an Alzheimer’s patient with diabetes.<sup>9</sup>

“Personalized healthcare of the future clearly needs to address co-morbidities,” asserted John Walsh, of the COPD Foundation. It will be important to recognize the interaction among different diseases and that personalized healthcare for one individual might require coordinating multiple treatments. Moreover, pharmacogenomics will play a crucial role in understanding efficacy and toxicity of drugs given to patients with co-morbid diseases.

### ***Benefits of Personalized Healthcare to Patients***

All respondents clearly understood the benefits of personalized healthcare described by the Personalized Medicine Coalition as the “right treatment for the right person at the right time.”<sup>10</sup> We found a consensus that it would be a significant advancement if the tools of personalized healthcare allow for earlier diagnosis and improved treatment success, including targeting drugs for use in people who will derive a benefit.

We found a dearth of understanding among respondents in the role personalized healthcare can play in avoiding drugs that will lead to adverse events. The removal of Vioxx from the market and the black box warning placed on other drugs attract big headlines in the media and patients are aware of these events. However, they do not always recognize that the identification of a drug causing severe side effects in a population subset is an advance in personalized healthcare. Some saw that future

<sup>8</sup> Personal communication with John Walsh, President of COPD Foundation, September 4, 2008.

<sup>9</sup> Personal communication with Jennifer Zeitzer, Associate Director, Federal Policy, Alzheimer’s Association, September 10, 2008.

<sup>10</sup> See the Personalized Medicine Coalition report, The Case for Personalized Medicine 2006, [http://www.personalizedmedicinecoalition.org/communications/pmc\\_pub\\_11\\_06.php](http://www.personalizedmedicinecoalition.org/communications/pmc_pub_11_06.php).

relabeling or warnings for medications could serve as teaching opportunities for the patient community about what personalized healthcare can offer.

**Personalized healthcare has been defined as offering the promise of better care delivered more efficiently.** In areas such as oncology, patients want better assurances that treatments will work for them. Particularly in cancer treatment, patients do not always have confidence that their treatment will be effective, thus they fear the side effects of a treatment that may not yield benefit. In the breast cancer community, survivors are focusing more on survivorship care plans that help them track the impact and potential for side effects of the treatments on their health down the road.<sup>11</sup>

### *Impact of Personalized Healthcare on Costs*

Many respondents felt it is difficult to completely predict how personalized healthcare will unfold in the next 10-15 years and its impact on escalating healthcare costs. If personalized healthcare can help reduce costs, everyone regarded this as a positive and important benefit. Most respondents mentioned that they saw costs going up before going down as a result of personalized healthcare.

Patient advocates believe that personalized healthcare will ultimately lower costs by:

- reducing the need for repeat visits,
- reducing the number of adverse events and some hospitalizations, and ultimately resulting in better health outcomes,
- saving patients and providers time, money, and wasted effort since most drugs are not working in some subset of certain patient populations, and
- providing tools that give providers information about which subpopulations are likely to respond to therapy.

Respondents thought the cost to develop targeted, personalized therapies could be higher than the costs of developing existing treatments and might be labeled for use in smaller market sizes which could increase drug pricing. Thus there is concern that as therapies become more tailored, they may also become more expensive, and that investment in drugs for lower incidence populations won't get pursued. Uncertainty about how payers will integrate targeted therapeutics into coverage and reimbursement decisions exists.

### *Concerns about Personalized Healthcare*

**Drug Development.** Respondents acknowledged that the drug development models that currently exist will have to evolve to prepare for the personalized healthcare advances. There needs to be a process in place that considers the implications of the creation and characterization of subgroups of patients within a disease by both pharmaceutical and biotechnology companies and by the U.S. Food and Drug Administration (FDA). There

<sup>11</sup> Personal communication with Elizabeth Thompson, Managing Director, Public and Medical Affairs, Susan G. Komen for the Cure, September 18, 2008.

are opportunities within FDA to make sure all the required policies are in place to promote the advancement of personalized healthcare practices. A robust post-marketing system needs to be in place to identify safety risks as these drugs are used by a more heterogeneous population. Also, the research building blocks with FDA drug safety efforts need to be aligned to learn more about how drugs are experienced in a large population.

From the scientific perspective, data continues to come in on most diseases about the variability within the particular disease class. Scientists and advocates are increasingly discussing the possibility of different subtypes of their particular disease areas. For example, Parkinson's disease (PD) patients present to their doctors with their own personal mix of symptoms that roughly categorize them as PD patients. When treated, these patients often experience highly varied responses to medications. This known heterogeneity is still generally overlooked if not ignored as treatment protocols consider all these patients in a single category of disease. In fact, recent "failures" in clinical trials in PD might more appropriately be viewed as "inconclusive" findings with pockets of treatment success but insufficient (underpowered) evidence to propel the trial to its next stage of investment and/or investigation. The Michael J. Fox Foundation for Parkinson's Research (MJFF) is focused on attempting to better understand and characterize the "subtypes" of disease with the particular goal of improved patient selection for clinical trials in mind.<sup>12</sup>

Also, some respondents raised the question of what needs to be done to facilitate the process of subgroup analysis and how to study different populations that respond differently to treatments. It was also acknowledged that even in areas where there are some targeted therapies identified, more research is needed. The work is not over when the initial finding is made. For example, new analysis of the data shows that women taking Tamoxifen can metabolize the drug differently.<sup>13</sup>

"It is clear we need to find ways to do clinical trials that are faster and cheaper," asserted Debi Brooks, Co-Founder of MJFF. "One of our strategies is to fund creation of tools that can contribute to improved trial design in the first place." In addition to the continued work to identify subtypes of disease, MJFF has a collaborative project underway where the Parkinson's Institute and the company 23andMe are working to validate web-based surveys that could provide a proof-of-concept for tools to enable more robust data collection in the clinical trials process. In smaller disease populations that have potential subpopulations of disease, improved and innovative clinical trial design to increase the power of smaller sample sizes will help researchers complete studies faster.

Additionally, until we have diagnostics that can identify who should receive which drug, patients want an improved adverse events reporting system that can contribute to research

<sup>12</sup> Personal communication with Debi Brooks, Co-Founder, Michael J. Fox Foundation for Parkinson's Research, September 4, 2008.

<sup>13</sup> Personal communication with Elizabeth Thompson, Managing Director, Public and Medical Affairs, Susan G. Komen for the Cure, September 18, 2008.

and development of such tests. One way to better understand extrinsic factors like drug-to-drug interactions, medical practice, diet, alcohol use and intrinsic factors like gender, genetics, and race is to establish systems that improve adverse event tracking. Currently the FDA is actively embarking on this task. In May 2008, FDA launched its Sentinel Initiative with the goal of creating and implementing a national, integrated, electronic system for monitoring product safety. This effort will strengthen FDA's ability to monitor the performance of a product throughout its life cycle and enable real-time reporting of potential safety signals for medical products currently on the market.

Some respondents are concerned about genetic testing companies and want assurance these tests are accurate and that support systems and providers are ready and waiting after patients take the tests. The regulatory framework for these testing companies is still being created; the FDA does not evaluate these tests for accuracy, though a federal panel recently recommended stepped-up oversight. Different states have different regulations about the ordering of tests and the involvement of medical professionals; several states have ordered direct-to-consumer testing companies to stop selling their tests to residents of their states until they prove they have met that state's quality standards (which several companies subsequently did and received licenses to operate). Two major associations for genetics professionals disagree about whether any genetic tests are appropriate for sale directly to consumers without a medical intermediary. While regulators and medical professionals deliberate, the popularity of genetic testing is undeniably increasing, helped along by "genetic social networking" Web sites and program launches at venues such as the Mayo Clinic, Canyon Ranch Institute, and the Cleveland Clinic, opening whole new frontiers in the consumer information revolution.

**Gatekeepers.** Many respondents identified their patients' need for a "medical home" to provide coordinated and targeted care. One patient said, "So, while providing more detailed tracking is helpful, one also needs a doctor who is receptive to that same tracking." Some saw how this approach may create a situation where the provider serving as a gatekeeper may instead block or slow access to care. As patients have more and more access to information, and as they have mobilized, they want access to providers that will discuss options and a gatekeeper may stand in the way of that. Similarly, as therapies start to become available for subgroups of patients, there is concern about how the payer community will react. One respondent said, "What if treatment is only available if it works for everyone with our disease?"

There has been a lot of discussion in the past couple of years about comparative effectiveness. This is the approach that many healthcare stakeholders are turning to as a possible solution to curb healthcare spending. Comparative effectiveness research seeks to provide a cost-effective and efficient approach to identifying the best in drugs, devices, biologics, and medical procedures. However, as the drumbeat for comparative effectiveness intensifies, it is important to ensure that the law of averages does not steer decision-makers away from treatment that demonstrates true patient benefit. Comparative effectiveness needs to allow for new research findings, as well as allow for diseases that may ultimately encompass hundreds of genetic variations and subtypes.



**Privacy.** There is lingering concern about whether individual test results and large datasets with personal information will be used against people for employment or insurance purposes. One respondent said that the passage of the Genetic Information Nondiscrimination Act (GINA) hasn't assuaged those fears. (For more information about GINA, see page 18). However, a majority of the patient organization leaders we spoke with felt that privacy needed to be dealt with and closely monitored, but that it should not interfere with scientific and healthcare delivery advances. One respondent said, "We don't want the politics of fear of privacy breaches to get in the way of the needed advances."

Advances in 21<sup>st</sup> century healthcare will heavily depend on advances in genetic research and other medical solutions that fuel the search for new treatments and cures. The passage of the GINA allows patients to more confidently participate in studies that search for linkages between genes and disease, to enroll in clinical trials for new targeted drugs, or to provide samples for DNA analysis to optimize their own disease prevention and treatment.

Due to the lack of EHRs in many care systems, respondents noted that often patients' records were private, even to them. Some felt that the general consumer population was more concerned about privacy than patients, many of whom understand the value that pooled data can provide to the understanding of their disease. However, some still have concerns about posting their data onto some of the online personal health records systems. One patient said, "One of the risks that is going to emerge very quickly is the privacy status of medical records held by companies which function as control repositories."

The impact of the Health Insurance Portability and Accountability Act (HIPAA) and privacy were raised in the context of conducting research studies. In many disease areas, sample collection is becoming standard practice, and yet there is still confusion of what is and is not allowable under HIPAA. There was concern about the impact of restrictions on the speed at which research can be conducted, and the fact that patients continue to lose ground in battling their conditions with these delays.

### ***Educating Patients***

In order to be truly effective with optimal impact, patient-centric and proactive healthcare practices must be supported by comprehensive education and communications efforts. The general public needs to understand genetic medicine - what it can and cannot do - and not be afraid of the power of this area of science. Healthcare providers need to be able to sift through the most recent advances in medicine and translate these into real-world scenarios, carefully putting the most promising developments into context for each patient. The doctor-patient relationship needs to be defined by clear and transparent lines of communication. It is vital that new developments brought about by personalized medicine approaches be managed and translated responsibly and effectively into tangible treatment protocols when appropriate.

Most felt that it would not be difficult to educate patients about the advances that will come from personalized healthcare. Patients are hungry for information, and many survey respondents mentioned how self-motivated their constituencies are. Many respondents cited the high motivation their constituencies have to accelerate the research process in order to have better treatments available.

One respondent felt that trusted messengers (e.g., medical associations, advocacy groups, the U.S. Surgeon General) could lead national efforts to educate consumers. It was pointed out that a major risk relates to unrealistic expectations by the patient. This patient said, “Sometimes, even with the right diagnosis and treatment, I won’t get better.”

It was felt that all stakeholders involved need to carry the messages to patients about the potential benefits personalized healthcare offers. Providers ranging from primary care physicians to specialists and all other providers that intersect with the patient communities need to be given tools to help them communicate these messages.

There is still a lot to learn about how patients will respond to detailed genetic profiling as that becomes a reality. One person said, “The jury is still out about how this will really be rolled out over time and how patients will manage this new information.”

Some groups talked about needing more documentation of successes in the area. “We need to have the demand for the science defined publicly so it is constituent driven.” Another respondent spoke of the flat funding for NIH and the concerns that it raises for the future pace of scientific advances. **These comments speak to the need to engage fully with patients to be research advocates and suggests that the more motivated a patient is to get involved in a patient-oriented organization, the more likely they will be engaged in personalized healthcare.**

#### **IV. Potential Impact of Personalized Healthcare in Healthcare Delivery**

There are several areas of healthcare that will be significantly affected by the adoption of a personalized medicine approach. Most notably, personalized healthcare alters the traditional model of healthcare delivery, shifting some responsibility toward the consumer while simultaneously requiring healthcare providers to process even more information. It also raises questions about:

- when evidence is sufficient for use in health and disease management;
- how best to gather and assess evidence about effectiveness and efficacy; and
- how to appropriately regulate drugs used in personalized medicine.

#### ***Use of Genomics and Biomarkers to Predict Disease***

An individual’s genetic and molecular profile, if accurately assessed, has the potential to predict predisposition to certain chronic diseases – for example, prostate cancer, glaucoma, Alzheimer’s disease, or heart disease – as well as guide disease prevention strategies and more effective use of therapies. Currently, many of these tests are predictive, rather than diagnostic, which means results are provided to otherwise healthy

consumers as probabilities, or relative risks for an individual versus the general population. Most tests rely on SNP analysis or whole genome scans but others are based on non-DNA biomarkers associated with a particular pathological or physiological state.

As the technology for such testing – in particular genomic analysis – has advanced, the costs have decreased, which has spawned the growth of a new industry focused on personalized genomic services, frequently marketed directly to the consumer. Because in most cases the consumer can purchase the test and receive results without the direct involvement of a personal healthcare professional, several concerns have arisen.

- 1) Is the scientific evidence supporting the genomic-disease associated information sufficient for clinical use?<sup>14</sup>
- 2) Are consumers able to appropriately and effectively use such information in their own healthcare management?<sup>15</sup> and
- 3) Are healthcare providers sufficiently proficient in the application of probabilistic genomic information to respond to patient queries and develop a healthcare management plan appropriate for individual patients?<sup>16</sup>

Those advocating for more consumer involvement in test decisions believe that the slow pace of provider uptake and professional education, combined with more focus on consumer education and autonomy warrants such an approach.<sup>17</sup>

### ***Pharmacogenomics***

A specific field in personal medicine is pharmacogenomics, sometimes called molecular medicine. Pharmacogenomics is based on identifying genetic factors that directly influence a person's response to a drug. It has the potential to enhance understanding of disease etiology and diagnosis as well as the determinants of drug effects so better prescribing decisions can be made. What makes pharmacogenomics both unique and a challenge is that it melds the worlds of diagnosis and treatment in new and different ways. It is an application of genetics and pharmacology that brings genetic testing into the purview of primary care, well beyond the more traditional bounds of rare diseases, where genetic testing has its historical roots.<sup>18</sup>

<sup>14</sup> Cecile A et al., "A Critical Appraisal of the Scientific Basis and Personalize Health Interventions," *The American Journal of Human Genetics*, 82:593-599, March 2008.

<sup>15</sup> Gosline A, "Genome Scans Go Deep into Your DNA," *Los Angeles Times*, April 14, 2008, [www.latimes.com/features/health/la-he-genome14apr14,0,2443364.story](http://www.latimes.com/features/health/la-he-genome14apr14,0,2443364.story).

<sup>16</sup> Harvey EK et al., "Providers' Knowledge of Genetics: A Survey of 5915 Individuals and Families with Genetic Conditions," *Genetic Medicine* 9(5): 259-267, 2007; Scheuner, et al., "Delivery of Genomic Medicine for Common Chronic Adult Diseases," *Journal of the American Medical Association* 299(11):1320-1334, 2008.

<sup>17</sup> Wolfberg AJ, "Genes on the Web—Direct-to-Consumer Marketing of Genetic Testing," *New England Journal of Medicine*, 355(6):543-545, 2006.

<sup>18</sup> Hanna KE, "Pharmacogenomics and the Evolving Regulatory Paradigm," *Research Practitioner* 8 (6):210-216, November-December 2007.

It is likely that in the future, drugs incorporating pharmacogenomic data will involve both a therapeutic agent and diagnostic test, wherein the diagnostic test will precede the prescription, which suggests a new model for healthcare delivery. Because pharmacogenomics can help physicians determine whether a proposed drug therapy is relevant to a given patient, this approach to clinical care has the potential to enhance preventative medicine and reduce the level of trial-and-error in patient management. As with the use of personalized genomics testing services, pharmacogenomics will increase the volume of information that will have to be processed and used by patients and their healthcare providers.

## V. New Approaches and Opportunities to Transform the Drug Development Process

***“...in the next 15 years the pharmacopoeia that we use for treating lots of disease will be very heavily influenced by the things we’re discovering right now about the molecular basis of disease. But that has the longest lead time, and so it won’t happen overnight for many conditions.”***

*-- Francis Collins, former Director of the National Human Genome Research Institute at the NIH<sup>19</sup>*

### ***New Approach to Clinical Trials***

One of the challenges of personalized healthcare lies in assessing outcomes. First, because some of these interventions are being offered directly to the consumer it will be difficult to follow consumers to assess effectiveness and other outcomes. Thus, it will be critical that there be some publicly funded studies in these areas.

Second, because the very nature of clinical evidence will become more focused on individuals and subpopulations, personalized healthcare challenges the notion of randomized clinical trials as the gold standard for testing the safety and efficacy of new diagnostics and drugs. Simple reliance on biomarkers may be a poor method of predicting outcomes.

At least for some time it will be critical to evaluate large numbers of people before understanding the relative role of any given variant and its significance in personalized healthcare. Weak predictability combined with our lack of understanding of the causal relationship between genes and drug responses makes it difficult and costly to conduct appropriate validation studies. These studies are probably going to have to be large-scale, prospective studies that measure genetics and other biomarkers over time and follow up with patients for long-term outcomes.<sup>20</sup>

As such, analyzing evidence emerging from personalized medicine will require a different set of skills than those used in traditional clinical trials, combining diagnostic evidence with safety and efficacy evidence. Research will be needed to develop the best

<sup>19</sup> Collins F, “Genomic Research and Personalized Medicine: An Expert Interview with Francis Collins, MD, PhD.” Medscape Genomic Medicine, May 8, 2008.

<sup>20</sup> Garrison LP and Austin MJ, “Linking Pharmacogenetics-Based Diagnostics and Drugs for Personalized Medicine,” Health Affairs 25(5):1281-1290, 2006, p.1285.

methods for collecting and analyzing evidence and large numbers of subjects will be needed for clinical trials.

### ***Seizing Proven Opportunities***

While nearly 10 percent of the drugs approved by the FDA include pharmacogenomic information in their labeling, only four have a sufficient body of evidence to support a requirement for genetic testing before treating a patient.<sup>21</sup> Many other drug labels reference validated biomarkers and associated diagnostic assays, but these are only ‘recommended’ to provide additional information—not because evidence has shown their impact on outcomes to be variable or unreliable, but because there is *no evidence regarding outcomes at all*. This highlights a fundamental imbalance in the progress of pharmacogenomic research: more and more studies are linking genotype to the mechanisms of drug metabolism and/or efficacy, but few are taking the critical next step of tying modified dosing or selective use of drugs based on genotype to improved patient outcomes. Stakeholders have identified the lack of clinical evidence base as a critical barrier to integration of personalized medicine into routine practice.<sup>22</sup> Making this connection to outcomes is necessary to realize personalized medicine’s promise.

The stakes are even higher since many of the drugs for which pharmacogenetic factors have been identified are often dangerous to patients and adverse reactions can be lethal. The FDA’s list of drugs with genetic biomarkers includes chemotherapy agents, anticoagulants, and neurologic agents—drugs whose side effects would exclude them from use were it not for the lack of suitable therapeutic options for patients with grave conditions. With more than 770,000 injuries and deaths due to adverse drug reactions and medication errors each year<sup>23</sup>, elucidating whether genetic information can improve outcomes and reduce some of these events is critical to ensuring the safety of patients who take these drugs.

A growing body of research reveals the great promise of using an individual’s genetic information to guide his or her care; the next step for us is to seize that demonstrated opportunity by confirming whether this information can effect real change in short- and long-term patient outcomes. We can save patients’ time by building the evidence base as soon as possible so that caregivers can act on the promise of personalized medicine. We can save patients’ lives by defining how genetic tools can ensure a patient’s treatment is not only timely and beneficial, but *safe*.

## **VI. Making Personalized Medicine a Reality: The Need to Address Privacy**

<sup>21</sup> See FDA’s Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels, [http://www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm).

<sup>22</sup> Deverka PA et al., “Integrating Molecular Medicine in the US Healthcare System: Opportunities, Barriers and Policy Challenges,” *Clinical Pharmacology & Therapeutics*, 2007; 82(4): 427-34.

<sup>23</sup> See Agency for Healthcare Research and Quality report, Reducing and Preventing Adverse Drug Events to Decrease Hospital Costs. Research in Action, Issue 1, March 2001, <http://www.ahrq.gov/qual/aderia/aderia.htm>.

***“These are catch-all diseases (e.g., cardiovascular disease, Alzheimer’s disease, rheumatoid arthritis, and cancer) that look the same, but when you scratch below the surface, you begin to understand that the underlying physiology of similar phenotypes can be fundamentally different.”***

-- John Sninsky, Vice President of Discovery Research at Celera<sup>24</sup>

Precious patient resources are lost to medical research if individuals fear that genetic information, test results, or electronically stored health records might be used against them by insurers or employers. Public opinion has long reflected widespread anxiety about misuse of personal health information.

In a 2004 survey of 470 people with a family history of colorectal cancer, for example, about half said their concern about genetic discrimination was high, and that they would be significantly more likely to pay for genetic testing out of pocket, use an alias, or ask for test results to be excluded from their medical record.<sup>25</sup> Dr. Francis Collins, former Director of the National Human Genome Research Institute, has said that “at the NIH, fear of genetic discrimination is the most commonly cited reason that people decline to participate in research on potentially life-saving genetic testing for colon cancer and breast cancer. One-third of eligible participants have declined on this basis.”<sup>26</sup> People have been reluctant to know and act on genetic health risks, to their own detriment and society’s as a whole.

A patchwork of legislation at the state and national levels has tried to regulate the use and disclosure of personal health information, most prominently the 1996 HIPAA, which regulated the use and disclosure of such information by certain “covered entities.” Successfully navigating HIPAA and human research protections will be critical to advancing the science of personalized medicine.<sup>27</sup> And in 2008, after 13 years of effort, Congress passed and the President signed the GINA, which advocates have called the critical civil rights bill for the genome era.

To summarize, GINA:

- Prohibits use of an individual’s predictive genetic information in setting eligibility or premium or contribution amounts by group and individual health insurers;
- Prohibits health insurers from requesting or requiring an individual to take a genetic test;
- Prohibits use of an individual’s predictive genetic information by employers in employment decisions such as hiring, firing, job assignments, and promotions;
- 

<sup>24</sup> Mullin R, “Personalized Medicine,” Chemical & Engineering News, February 11, 2008.

<sup>25</sup> Apse KA, et al., “Perceptions of genetic discrimination among at-risk relatives of colorectal cancer patients,” Genetics in Medicine, 6:510-516, 2004.

<sup>26</sup> Kibak P, “After long wait, GINA becomes law,” Clinical Laboratory News, July 2008.

<sup>27</sup> Carhart S, “Coming Century to Witness Major Changes as Hospitals Adapt to Personalized Medicine,” BNA’s Health Law Reporter, 17(25): 1155, 2008.

- Prohibits employers from requesting, requiring, or purchasing genetic information about an individual employee or family member.<sup>28</sup>

The health insurance provisions of the bill will take effect in May 2009 and the employment provisions will take effect in November 2009. GINA does not apply to members of the U.S. military, or to other forms of insurance such as life, disability, or long-term care.

It is expected that passage of GINA will boost demand for genetic tests, leading to improvements in care and more participation in research that involves the collection of genetic information. But the passage of legislation is not enough. There has to be effective education of the public and providers about the protections that GINA confers. That includes compelling demonstration of the benefits genetic testing and personalized medicine will bring to them as individuals, as well assurance that new tests and personalized treatments will be paid for.

In addition, the application of GINA's protections must be clear and consistent. Lessons must be learned from the experience with HIPAA, whose provisions regarding privacy have been misinterpreted and over interpreted in ways that have been detrimental to the conduct of medical research. In a 2007 survey published in the *Journal of the American Medical Association*, more than two-thirds of epidemiologists reported that the HIPAA Privacy Rule has made research more difficult, adding a great deal of cost and time to study completion without a countervailing positive influence on subjects' privacy.<sup>29</sup>

And we need to continue to look beyond GINA at additional ways in which privacy concerns must be addressed in order to promote and facilitate the development of personalized healthcare. For instance, not addressed by GINA are all the security and privacy implications of the large databases of medical records tied to biological samples that will be required for the promise of personalized medicine to be realized.

## VII. Genetic Literacy and the American Public

Patient-centered care requires that patients be informed, proactive partners with their physicians when facing health decisions. But a major hurdle for patient-centeredness in personalized medicine is a lack of 'genetic literacy' or a fundamental understanding of genetics and health in the general public. Informed patients are critical to patient-centered care, but as personalized medicine techniques become more sophisticated and information more complex, caregivers will face steeper challenges in communicating effectively with patients of all education levels and backgrounds. Improving the genetic literacy of the general public will be an important step in empowering patients to seek and understand personalized medicine.<sup>30</sup> As early as 1994, the National Research

<sup>28</sup> See Genetics and Public Policy Center, [www.DNAPolicy.org](http://www.DNAPolicy.org)

<sup>29</sup> Ness R, "Influence of the HIPAA privacy rule on health research," *Journal of the American Medical Association*, 298(18):2164-2170, 2007.

<sup>30</sup> Haga, SB, "Teaching resources for genetics," *Nature Reviews Genetics*, 7, 223–229, 2006.

Council (NRC) was making calls for a "genetically literate public that understands basic biological research, understands elements of the personal and health implications of genetics, and participates effectively in public policy issues involving genetic information."<sup>31</sup>

Unfortunately, the past 14 years have not seen the NRC's vision realized. A 2006 study on public attitudes about evolution showed that on an index of genetic literacy, American adults scored a median of 4 on a 0-10 scale, indicating that many adults are not well-informed of genetics principles.<sup>32</sup> Some studies have shown that minority populations of diverse cultures, in particular, have limited genetic knowledge despite a desire to know more about genetics and health.<sup>33</sup>

There are a number of programs aimed at addressing these deficits in genetic knowledge in the public: for example, March of Dimes has launched its Consumer Genetics Education Network (CGEN) Project, a five-year program to address genetic literacy in underserved populations and to increase access to culturally and linguistically appropriate genetics education programs and services.<sup>34</sup> The Health Resources and Services Administration funds the activities of the 'Consumer Initiatives for Genetic Resources and Services', a discretionary grant program through the Maternal and Child Health Bureau. Programs receiving grants provide education about genetics and genetic testing to patients, usually in the context of specific screening tests or conditions.<sup>35</sup> Genetic Alliance is one of the recipients of MCHB grants to improve genetic literacy, and is also working with funding from Centers for Disease Control and Prevention to develop the Access to Credible Genetics (ATCG) Resources Network, a genetics information resource for patients with rare genetic diseases and their families and physicians.<sup>36</sup> The National Human Genome Research Institute (NHGRI) at the National Institutes of Health also has active grants awarded to projects addressing genetic literacy among underserved groups.<sup>37</sup>

## **VIII. Personalized Healthcare: A Patient-Centered Action Plan**

<sup>31</sup> National Research Council report, *Assessing genetic risks: implications for health and social policy*, 1994, Washington, DC: National Academies Press.

<sup>32</sup> Miller JD, et al., "Public Acceptance of Evolution," *Science*, Vol. 313. no. 5788, pp. 765 – 766, August 11, 2006, Vol. 313. no. 5788, pp. 765 – 766.

<sup>33</sup> Catz DS, et al., "Attitudes about genetics in underserved, culturally diverse populations." *Community Genetics*. 8(3):161-72, 2005.

<sup>34</sup> See March of Dimes CGEN Project Website

[http://www.marchofdimes.com/professionals/15829\\_29466.asp](http://www.marchofdimes.com/professionals/15829_29466.asp)

<sup>35</sup> Health Resources and Services Administration, Maternal Health Bureau, Consumer Initiatives for Genetic Resources and Services Abstract search, <https://perfddata.hrsa.gov/mchb/DGISReports/Abstract/AbstractSearch.aspx>, Last Accessed September 10, 2008.

<sup>36</sup> See Genetic Alliance Access to Credible Genetics Resources Network <http://geneticalliance.org/atcg>.

<sup>37</sup> See National Human Genome Research Institute Active Grants Database, <http://www.genome.gov/10001799> Last accessed August 25, 2008.



Personalized healthcare promises to be curative, predictive, and preventive. Our qualitative survey of patient organizations and patients themselves found a shared anticipation of the cutting-edge possibilities of personalized healthcare advances, especially as seeds of innovation yield tangible tools that move this approach forward. However, patient involvement is central to generating a sea-change in the traditional model of healthcare delivery.

Realigning the promise of personalized healthcare requires effectively and efficiently shifting some responsibility to the consumer while simultaneously requiring healthcare providers to process even more information.

We offer a framework for multiple stakeholders in the healthcare delivery system to act on to make personalized healthcare a reality:

- **Involve Patients in Medical Research.** An individual's genetic and molecular profile has the potential to predict predisposition to certain diseases, guide prevention strategies, and develop customized therapies. It is crucial for patients to understand their value to medical research and to actively participate by donating their biological specimens, being a part of clinical trials, and advocating for the use of EHRs. Accelerating and rewarding patient involvement in medical research will allow us to seize personalized healthcare's promise to affect real change in short- and long-term patient outcomes.
- **Transform the Drug Development Process.** Personalized healthcare challenges the long-held belief that randomized clinical trials are the gold standard for testing the safety and efficacy of new diagnostics and drugs. Understanding evidence emerging from personalized medicine will require a different set of skills than those used in traditional clinical trials, combining diagnostic evidence with safety and efficacy evidence. One of the challenges of personalized healthcare lies in assessing outcomes because some of these interventions are being offered directly to the consumer and because the very nature of clinical evidence will become more focused on individuals and subpopulations.
- **Protect Patient Privacy.** Key to the widespread adoption of personalized healthcare is addressing public anxiety about misuse of personal health information. The privacy protections realized through the passage of GINA will lead to improvements in care and more participation in research that involves the collection of genetic information. We need to ensure that the application of GINA's protections is clear and consistent.
- **Focus on and Deliver Patient-Centered Care.** Personalized healthcare elevates the role of the patient to that of data source, proactive partner, and decision-maker. The role of the healthcare provider will evolve as well. The provider becomes the information filter, translating medical breakthroughs into real-world scenarios applicable at a personal level. However, our ability to deliver patient-centered care, and therefore personalized healthcare could be held back by the existing insufficiencies within our healthcare system.

# Community Case Studies



# **Baylor College of Medicine**

## Houston, Texas

**Peter Traber, MD**  
*President and CEO, Baylor College of Medicine.*

### **OVERVIEW**

- Baylor College of Medicine (BCM) seeks to establish an institution-wide approach to personalized medicine with the three core values of quality, service, and individualized care that ensures that each patient receives the proper intervention or treatment at the right time based on his or her unique biology.
- The Personalized Medicine Alliance of BCM seeks to align the missions of the College and members of the community into a single vision of individualized patient care in the genomic age.
- BCM is actively working towards a future in which literacy about genomics and personalized medicine is broad-based in society, by adding innovative resources and programs across the educational spectrum.
- The Baylor Clinic and Hospital, with a planned opening in 2011, is designed *de novo* to combine the best in science, information technology and compassionate treatment for the kind of personalized medicine now possible and in readiness to implement future phases of genomic medicine.
- BCM has the breadth and depth in human disease genetics – from medical testing through basic genomics research – to fulfill the scientific promise of personalized medicine. The BCM chip, for example, is being developed as an important new tool for diagnosis and treatment.
- A key component of BCM's comprehensive personalized medicine program will be an information system that integrates electronic health records with other scientific data on a standardized platform to facilitate inter-institutional collaboration.

### **PHILOSOPHY**

Personalized medicine involves the tailoring of prediction, prognostication, diagnostics and therapeutics to the individual, based on that person's particular biological makeup, to ensure that the right thing is done for the right person at the right time. This requires not

only advances in medical technology, but also the coincident development of better information infrastructure, better integration of clinical and research efforts, continuing innovations in medical education, and finally, a deep relationship with the patient that makes that person a partner in the healthcare he or she receives.

Academic medical centers, such as Baylor College of Medicine (BCM), are not only especially qualified to forge a path towards this future, but they have a social obligation to do so. Academic medical centers bring vast experience in the rapid incorporation of research and clinical innovation into multiple levels of education; and, for personalized medicine to reach its potential, educating health care professionals and the general public to engage in a common dialogue will be as important as training the next generation of physicians. Furthermore, personalized medicine has the potential to form an attractive unifying vision for academic medical centers and for healthcare solutions more generally, by focusing the efforts of scientists, educators, and clinicians directly on the patient. Thus, Baylor College of Medicine's leadership seeks to establish an institution-wide approach to personalized medicine with three core values:

- **Quality:** Providing evidence-based care with the highest priority to patient safety, proven best practices and clinical outcomes.
- **Service:** Using processes and information that are convenient, easy, understandable and focused on the individual patient to provide an integrated healthcare experience.
- **Individualized Care:** Ensuring that each patient receives the proper intervention or treatment at the right time by understanding and taking into account the biology of that person.

Making significant progress towards the goal of personalized medicine will require the cross-institutional involvement of many individuals active in all three of BCM's missions of education, research and patient care. This poses an organizational challenge for institutions as complex as academic medical centers. To bridge gaps in philosophy and execution, BCM will establish a **Personalized Medicine Alliance** to include all members of the BCM community – physicians, students, residents, bench researchers, administrators, its eight affiliated hospitals and institutions as well as alumni and members of the community – in an evolving organization that can combine the best of genomic medicine with patient care. BCM views such an alliance, rather than a new department or center, as the most effective way to affect the culture across multiple activities in the institution.

Establishing the Personalized Medicine Alliance as a virtual presence at Baylor College of Medicine will provide an important nexus for future innovation and planning. As a measure of institutional commitment, The Alliance will be chaired by BCM's President and CEO and include experts and advisors from across the College. We plan to announce the Alliance as an entity during fall 2008 and begin actively recruiting partners from within the College and its affiliated institutions.

Using technology that will also evolve with the science, BCM seeks through its Alliance to make delivery of healthcare a personal experience from the moment a patient enters its

clinic and/or hospital. The genetic information that defines an individual will be only part of the picture. The Alliance also seeks to find ways to use that information that takes into account the needs and preferences of each patient, giving that person the best in personalized medicine.

We are designing the Baylor Clinic and Hospital, now under construction, from a blank slate to augment the goals of the Alliance, BCM and the patients who seek care from its physicians and institutions. In doing so, we hope to educate a new generation of physicians and allied health professionals. Achieving this goal at BCM involves more than developing a gene chip, a new hospital and clinic and an electronic medical record – all projects underway. It means bridging gaps within and outside of the institution itself in order to make medicine personal in an entirely new way, using the patient’s individual genetic code to define diagnosis, prevention and care for a lifetime.

## **HISTORY & RESOURCES**

Founded in Dallas in 1900 as a proprietary medical school, BCM affiliated with Baylor University in 1903. In 1943, it moved from Dallas to Houston and in 1947, occupied the first building of the actual Texas Medical Center. For many of the healthcare institutions that subsequently arose in the Texas Medical Center, an affiliation with BCM was a key driver of success. BCM became independent of Baylor University in 1969, leading to State support of medical education, enhanced federal funding, and a strong self-sustaining philanthropic Board of Trustees. This sparked a remarkable growth, particularly in research programs.

Today, BCM is affiliated with eight hospital or healthcare institutions, including Texas Children’s Hospital, the nation’s largest children’s hospital; the Harris County Hospital District and Ben Taub Hospital, where the indigent in the county receive care; the Michael E. DeBakey Veterans Affairs Medical Center, one of the best veterans institutions in the nation; The Institute for Rehabilitation and Research, a prominent site of rehabilitation medicine; The Menninger Clinic, a nationally ranked mental health facility; The Methodist Health System and St. Luke’s Episcopal Hospital, two of Houston’s largest private hospitals. It has academic affiliates across the state and works closely with NASA through the National Space Biomedical Research Institute.

BCM has a broad range of education, research, and patient care programs including 25 clinical and basic departments, more than 90 research and patient-care centers, over 2,000 faculty members, 650 medical school students, 600 graduate school students, 125 allied health students, 700 postdoctoral researchers, and over 1,000 resident physicians. The College receives more than \$230 million in research dollars from the National Institutes of Health and a total of approximately \$310 million in research funding.

Of particular relevance to the Personalized Medicine Alliance, is BCM’s proven expertise and experience in a continuum of basic biological, genetic, and genomic research and translation into clinical genetic testing. BCM’s Department of Molecular and Human Genetics is ranked first among similar departments in funding from the National Institutes of Health and is responsible for multiple groundbreaking contributions to both

understanding the genetics of disease and translating genetic discoveries into the clinic. The Medical Genetics Laboratories at BCM have been dedicated to providing high quality comprehensive diagnostic services for over 30 years. Finally, BCM's Human Genome Sequence Center (HGSC) was one of three teams leading the final sprint to complete the initial publically funded sequencing of the human genome, announced in June 2000. Last year, the Center, in collaboration with 454 Life Sciences, completed the annotated DNA sequence of Nobel laureate and DNA pioneer, Dr. James Watson. Since that time, the Center has continued to work towards increasing the speed and decreasing the cost of sequencing an individual genome.

## **CURRENT EFFORTS, CHALLENGES AND PLANS**

### **Education**

While academic medical centers advance patient care and research, the primary mission of medical schools is to educate the next generation leaders in healthcare and biomedical research systems. Academic medical centers are responsible for providing budding physicians with the tools necessary to navigate and lead a future of dramatic change.

Postgraduate medical education in specialties and subspecialties has been done essentially the same way for decades. To advance the training of individuals who will champion personalized medicine, BCM is exploring a Genomic Leadership Residency Program to enable young physicians to make use of the new technology and provide a basis for translating new information from bench to bedside. Training these young physicians in the Baylor Clinic and Hospital, which is expressly designed to foster this kind of work, will speed the integration of gene-based research into direct patient care in a compassionate and intelligent manner. The period of graduate medical education, when the direction of a young physician's practice patterns are set, provides the best possible "teaching moment" to move the way medicine is practiced into the next generation.

The vision is to develop a creative new approach to graduate medical education that focuses on preparing the next generation of clinician-scientists and academic leaders, who will lead the transformation of medicine in the 21<sup>st</sup> century. The BCM Genomic Leadership Residency Program would be open to any physician in its ACGME-specialties, functioning as a multi-year academic track graduate medical education experience with a fully integrated research component. Residents would enter the program through the clinical specialty of their choice and at the end of the residency, be board-eligible in the specialty they choose. While the new Baylor Clinic and Hospital – designed to foster personalized medicine – will serve as the residency's "home," residents will also rotate through affiliated institutions for a well-rounded experience.

Key characteristics of the Genomic Leadership Residency Program will include:

- A core curriculum in the science of genetics/genomics, molecular and cell biology, etc., with an emphasis on the translation of science to clinical practice;

- A core curriculum in leadership that emphasizes inter-personal and communication skills, ethics and professionalism, system-based practice, and approaches to quality assessment and clinical outcomes, with each curricular element addressed in the context of the unique issues and challenges presented by genomic medicine;
- A strong multi-disciplinary emphasis, with most of the above core curricular elements delivered across traditional specialty lines;
- A required one or two year research experience, inter-disciplinary in nature where appropriate, which will be fully integrated into the residency program at intervals that assure that graduating residents are fully prepared as both clinicians and scholars; and
- A core set of multi-disciplinary clinical rotations that provide opportunities to work across specialties in applying genomic diagnostic tools and therapeutic interventions to the care of patients.

Educating the next generation of leaders, however, is not enough. BCM views its educational mission as spanning the entire life cycle of education, from the earliest years in grade school through continuing professional education programs. BCM sees a future in which literacy about genomics and personalized medicine is broad-based in society as critical to the success of personalized medicine. However, informing academic peers, the general medical community and the community at large about the reality of personalized medicine today and its promise in the future looms as a major challenge for BCM and the personalized medicine community itself.

The majority of the healthcare and academic work force trained before the genomic era and lack knowledge of the building blocks of personalized medicine. Furthermore, there is skepticism and an incomplete understanding of the role genomics along with an improved information technology infrastructure will play in personalizing medicine, which threatens to block acceptance and hinder efforts to go forward. Educational programs at academic medical centers must establish a realistic perspective on the opportunities provided by personalized medicine and a general timeline for reaching goals. Moreover, education cannot be focused at only a single level, but rather must be distributed across the spectrum of education, including training of teachers. Finally, there is the challenge of organizing the ever advancing information in this field so that it can reach the intended audience and be authoritative and realistic in its assertions.

BCM is addressing these challenges by incorporating the building blocks of personalized medicine across a wide range of educational programs (see Table 1). This includes revising both formalized curricula – from undergraduate genetics courses to continuing medical education accreditation – and more informal opportunities in the form of web-based seminars and novel educational tools for younger students. We are also exploring ways to structure information and educational materials so that learners can tailor their experience by choosing from a broad range of educational opportunities.

Through these kinds of educational and community outreach initiatives and indeed, through the Personalized Medicine Alliance, BCM hopes to do its part in creating a culture that not only accepts personalized medicine but also anticipates its forward progress.



**Table 1 Baylor College of Medicine's Educational Objectives for Personalized Medicine**

<b>Constituency</b>	<b>Educational Objective</b>	<b>Means to achievement</b>
<i>K-12 students and teachers</i>	<i>To teach the concepts in genetics and molecular biology that underlie personalized medicine, in order to advance quality teaching and learning in science and health as early as possible in the educational process, and promote access to careers in science and medicine.</i>	<p>BCM's <a href="#">Center for Educational Outreach</a> engages in a variety of projects at all educational levels. Examples include:</p> <ul style="list-style-type: none"> <li>• <a href="#">BioEd Online</a><sup>SM</sup> gives teachers instant access to reliable, cutting-edge information and educational tools for biology.</li> <li>• "A Pathway to Genomic Medicine" slide set and streaming video lecture</li> <li>• Web-based genetics course for advanced high school students</li> </ul>
<i>Medical Students</i>	<i>To teach preclinical genetics in the context of the research process and translation to the patient's bedside, in order that the next generation of physicians and clinical researchers has a solid foundation on which to build the future of personalized medicine.</i>	<ul style="list-style-type: none"> <li>• Revisions to the genetics and genomics curriculum are underway.</li> <li>• Foundational courses are taught by leading researchers and clinicians.</li> <li>• Scholarly project and research track options expose medical students to the research process.</li> </ul>
<i>Graduate Students</i>	<i>To develop Ph.D.-level researchers with an understanding of clinical medicine and the biology of disease states, in order to catalyze the effective movement of discoveries between bench and bedside that is critical to personalized medicine.</i>	<i>In 2005, BCM developed the Interdepartmental Translational Biology and Molecular Medicine Doctoral Program.</i>
<i>Post-graduate physicians</i>	<i>To prepare the future leaders of personalized medicine, in order to speed the integration of gene-based research into direct patient care in a compassionate and intelligent manner.</i>	<i>BCM is exploring a Genomic Leadership Residency Program as a multi-year academic track graduate medical education experience with a fully integrated research component.</i>
<i>Established physicians</i>	<i>To educate currently practicing physicians who may not be aware of the current boundaries and future promise of personalized medicine, in order to spread this promise beyond academic walls to benefit patients.</i>	<ul style="list-style-type: none"> <li>• In 2007, BCM initiated monthly genetic grand rounds for the Medicine Faculty.</li> <li>• BCM Center for Collaborative and Integrative Technologies and the Office of Continuing Medical Education is devising new content and seeking funding for its implementation.</li> </ul>
<i>General Public</i>	<i>To provide information about the foundations and possibilities of personalized medicine to the general community, while grounding the information in realizable goals.</i>	<i>BCM hosts multiple community events with varying audiences, including a regular seminar series entitled "Evenings with Genetics", where experts share the most current research, diagnosis and treatment information on genetic conditions.</i>

## Baylor Clinic and Hospital

To realize the goals of personalized medicine, healthcare delivery systems and facilities must be effectively linked to innovative physicians and healthcare workers, scientists and translational research, and education programs. However, the healthcare system in the U.S. suffers from many challenges including poor patient access, service, and education; ineffective integration of outpatient, diagnostic and inpatient care; poor information transfer and communication; and a general lack of good outcomes information. Although BCM has multiple outstanding affiliated hospitals, we decided that to deliver innovative personalized medicine to private adult patients, a new facility for faculty physicians was required.

The Baylor Clinic and Hospital, now well under construction with plans to open in 2011, promises to provide the kind of personalized medicine now possible and to be ready to implement new phases of genomic medicine as it matures. The new construction provides the opportunity to create a platform for personalized medicine without preconceptions or designs that impede the implementation of medical progress. In its first phase, Baylor Clinic and Hospital will have more than 1 million square feet with 252 inpatient beds (each of them private and 60 in intensive care units). There will be 15 operating rooms, 272 exam rooms and 270 faculty offices with specialties in cancer, cardiovascular disease, neurological disorders, transplantation and general surgery and medicine. It will encompass both outpatient and inpatient care in a coordinated fashion that links physicians and patients more closely than institutions in the past.



With today's technology, hospitals can become interactive entities. Technologies can see farther and deeper, hear more, and sense the environment at great distances while managing workflow and decision-making. Whether implementing robotic surgery technology, enabling sensor networks for tracking equipment, or providing physician-

patient videoconferencing, the Baylor Clinic and Hospital is committed to incorporating the best of technologies available today and expanding to those that come on-line in the future.

Of course, all the science and technology, bricks and mortar are a means to an end. That end is providing patients with care that is the best available, the most personal in understanding of their individual biology and understanding of their needs. In the final analysis, patients judge a healthcare facility not only on the quality of its technology, science and research, but also on the ability of its physicians, nurses and other staff to take care of them with humanity and compassion. Personalized medicine means more than a computer, a gene chip or a new test. It means a receptionist who answers the telephone and attempts to meet the patient needs. It is the physician who listens, and the nurse who remembers the salient points of the patient's problems.

A key ingredient of the new Baylor Clinic and Hospital will be state-of-the-art quality improvement, with constant data collection and measurement. Personalized medicine is not static, and patients will benefit only if we maintain efforts across the board – research, clinical and educational. First, however, we must define the most important outcomes to measure. Then we must put into place the means for gathering the data for those measurements in both a quantitative and qualitative sense. Most important, those measures must become transparent, and reported to the public on a regular basis. Where we fall short, we will change our procedures and activities.

Many challenges face a new hospital that seeks to deliver innovative services in addition to the difficulty of opening and operating a clinic and hospital in today's financial healthcare environment. New approaches, promoted by personalized medicine, will take time to implement and longer for reimbursement to come from third party payers. The current system rewards what is currently being done. However, we are confident that our approach will lead to irrefutable advances in healthcare. And as these outcomes become more apparent and the value of various undertakings are proven, BCM will move personalized medicine -- the technology, diagnosis and treatment – into its affiliate hospitals, making this care widely available across the community.

## **Human Disease Genomics and Diagnostics**

Advancement of genomic medicine is dependent on implementing diagnostic testing in patient care situations. There are many hurdles to achieve this including the need for extensive test validation and government regulatory approvals, clinical trials to assess efficacy, patient information and education, physician education, and strategies to receive reimbursement for offered tests. BCM has as a major strategic goal the marriage of its strengths in genomics and clinical medicine to advance the field of genomic medicine. The two general areas of discovery genomics and clinical genomic diagnostics will be instrumental in providing a scientific platform for clinical programs in personalized medicine in the Baylor Clinic and Hospital.

BCM has proven capabilities in discovering new links between genetics, treatment and disease. The BCM Human Genome Sequencing Center (HGSC) in collaboration with

faculty from Genetics and multiple BCM departments has several ongoing projects to apply sequencing information directly to human disease and many other investigators are pushing forward the frontiers of genomic discovery. BCM and the Personalized Medicine Alliance will continue to support and catalyze research in this area.

Capitalizing on what we know already about the links between genetics, disease, and treatment, BCM is currently implementing several advances in diagnostics. One project in general genomic testing that is of particular note is the BCM Chip.

The BCM Chip grew out of work begun with the BCM HGSC and the HapMap project, the first international effort to study human genetic variation. The HapMap project made use of technology developed by ParAllele, since acquired by chip developer Affymetrix. This chip platform technology was inspired by BCM scientists, John Belmont, MD/PhD, and Richard Gibbs, PhD, through brainstorming with ParAllele ways of simultaneously testing for thousands of gene variants that were relevant to adult disease.

A pilot project in the HGSC involving approximately 160 people last year enabled the team to test and refine a prototype chip. The latest version of the chip uses a platform from Illumina Corporation, and has migrated from HGSC into the clinical laboratories of the BCM Department of Molecular and Human Genetics.

In its current form, the BCM Chip contains a select, but not exhaustive, set of diagnostic aids:

- 2,300 assays devoted to pharmacogenetics relating to 32 gene variations that can affect the way individuals respond to different drugs. Understanding those genetic variations can help doctors determine optimal drug choice and dosing for individual patients.
- 800 tests for single nucleotide polymorphisms (SNPs) that increase the risk of common diseases such as breast and prostate cancer, coronary artery disease and type 2 diabetes. Information from the chip allows physicians to create a disease risk profile for individual patients.
- 400 assays that look at different SNPs used for human leukocyte antigen (HLA) typing. HLA typing is most important currently in transplantation as well as identifying the risk of some autoimmune disorders. However, some HLA types can also affect response to drugs, such as abacavir, a protease inhibitor used to treat HIV/AIDS.
- 3,300 areas on the chip will be used for the diagnosis of Mendelian disorders as well as cancer susceptibility, neurological disease (including Alzheimer's and Parkinson's disease) and cardiovascular disorders.

This potentially rich source of diagnostic information challenges bioinformaticians to render some 6,000 test results in a reportable digital form that can be used now as well as in light of future advances. Bioinformaticians are developing a system that can do almost all the interpretation of results automatically, filtering the relevant information into the patient's electronic medical record. Later, as information evolves, the database can be

configured to allow new information to “pop up” automatically as it proves important to the patient’s care.

In keeping with our ethic of personalized medicine centered around the patient, a collaborative effort involving the Cleveland Clinic and BCM is exploring patient understanding of the potential value and pitfalls associated with the kind of information produced by the BCM chip. In addition, this project seeks to quantify for the patients how the chip information fits into their medical care, avoiding the risk of over expectation or exposing information that could affect the patient’s peace of mind.

Plans are now underway to validate the chip and put it into the current Baylor Clinic for adult outpatient care before the end of the year. By 2010, we hope to have the BCM Chip in a stable configuration that meets the standard of the College of American Pathology. Its clinical role will become more apparent during that period.

## **Health Information Technology**

Underlying the promise of personalized medicine is a new information infrastructure that supersedes the current system of fragmented medical records, most not even in digital format.

Currently, a trip to the physician’s office might or might not be coordinated with reference to an available patient record. In the future, even before entering the hospital, a patient should be able to register via a Web portal, perhaps even interacting with established personal health record systems that are currently in development.

Personalized medicine will absolutely require a new infrastructure and methodologies for recording and tracking health information. Information systems must not only make patient data immediately available to the healthcare team, but also provide an effective interface between scientific and clinical information and analysis tools for exploring hypotheses. High throughput genetic sequencing, high throughput microscopy, high throughput functional magnetic resonance imaging scanning – all these techniques hold promise for the future of healthcare, but they carry a heavy burden of data. The system must manage information overload while linking all the necessary components to support scientific and clinical needs, including bio-banks, genomic and expression data, patient data and more. It must also make that information available to physicians across a host of platforms and in varying locales and situations.

Partnering with the Epic Systems Corporation, BCM is developing an interactive, responsive electronic health record that will not only meet current needs but also enable use of information in the future. For example, as new information about disease states and risks linked to genetic information becomes available, the Baylor College of Medicine EHR will alert physicians to new facts that may influence the way in which they provide care for a particular patient, perhaps influencing the choice of drugs or lifestyle advice that person receives.

Accomplishing this prototype system within the confines of an existing, antiquated structure with longstanding investment in old, tired systems would be almost impossible. However, the information structure of the Baylor Clinic and Hospital is a blank slate awaiting a new form of writing that will enable personalized medicine at its most efficient. Technology will be omnipresent but not overriding in the new hospital, with computer terminals available but not always visible as physicians, nurses and technicians provide the care that patients need and want in a compassionate manner with the best biological information available.

Once the system is established at the Baylor Clinic and Hospital, the College will collaborate with its affiliates, which are already developing or honing their own electronic medical records. Texas Children's Hospital and the Harris County Hospital District, which operates Ben Taub Hospital, have already selected Epic as their vendor, increasing the interoperability of those systems as they develop. Because electronic data is a moving target, establishing seamless systems will become easier as institutions seek to work together and regulation pushes most institutions toward similar solutions.

The EHR will need to feed into a larger system that brings multiple types of data together for analysis of healthcare quality and research efforts. Our goal is that the platform will support and use those systems that are being developed for standardization of data and inter-institutional collaboration, such as caBIG.

### **Bridging the Gaps**

The Personalized Medicine Alliance at BCM will face enormous challenges in providing guidance and leadership across the range of projects and plans that comprise our goal, which is nothing short of transforming the future of healthcare. We have provided a snapshot of the work we are doing to educate all constituencies, build a brand new hospital, maintain the pace of diagnostic and treatment progress, and incorporate that progress with patient data into a seamless electronic environment. To bring rapid advances on all fronts that still remain integrated in a larger picture of excellent patient care would be a impossible without an Alliance to bridge the gaps within and outside the institution and provide a continuity of vision for the future of personalized medicine.



# **National Cancer Institute**

## Bethesda, Maryland

### **The Biomedical Informatics Grid (BIG): A Platform for 21<sup>st</sup> Century Biomedicine**

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## **I. Personalized Medicine Requires a 21<sup>st</sup> Century Systems Approach**

### **Personalized Medicine as a New Biomedical Paradigm**

Personalized Medicine is a new paradigm in biomedicine. Its successful implementation requires integration of unprecedented amounts of information and diverse communities. The ability to collect, analyze, share, and integrate massive quantities of biological and clinical data in real time is a prerequisite for Personalized Medicine.

Biomedicine is a complex system. There are key interdependencies between the sectors that compose this complex system. Personalized Medicine's goal is to transform this system and must therefore recognize and embrace its complexity. Key opportunities to create a self-sustaining Personalized Medicine ecosystem come from understanding resource and information flows within the larger system.

### **Strategies for Addressing Complexity.**

Industry provides best practices for active design of complex systems. First, best practice requires one to recognize the system as a whole. Next, it identifies the interfaces between the components. Within the boundaries of the interfaces, individual components are developed and manipulated iteratively and incrementally. It is also important that initial development occur in a limited context, but one with sufficient complexity that it faithfully captures the complexity of the system component. Finally, additional complexity is also added incrementally with the controlled expansion of scope. This approach permits rapid incremental success without being stymied by the complexity of having to "boil the ocean."

### **The Essential Role of Information Technology.**

The daunting complexity of the personalized medicine ecosystem makes the use of information technology critical. But information technology within the biomedical enterprise has been slow to develop and is rarely connected between laboratories even within a single institution, much less between different institutions. In contrast with other national efforts, such as in defense or federally-funded physics research, the U.S. biomedical research enterprise has never had any such information technology system.



Thus, to address the complexities of cancer and these discontinuities of the research process, a 21st century biomedical enterprise requires *interoperability*; that is, access to integrated tools to collect, analyze, and share data in standardized formats. This interoperability is a means to link together all the scientists, clinicians, patients, and other participants so that they can share such standardized information rapidly.

The current generation of internet and world wide web technologies makes information technology approachable to biomedicine. Information technology is critical to the interface connecting the components of the biomedical ecosystem. It enables efficient operations within components.

### **A Systems View of Personalized Medicine Multidimensional Stakeholder Ecosystem**

The full ecosystem of Personalized Medicine encompasses members of the axes of biomedicine. It includes researchers, physicians, and consumers as participants. The researcher category includes discovery, translational, and clinical arenas. In an alternative axis, the ecosystem includes the academic, not-for-profit, commercial, and government sectors. A complete survey of the ecosystem also contains gatekeepers, such as regulators and payers.

### **Connectivity Through Information Technology**

The needs of Personalized Medicine for information-sharing are accommodated by best practices in information technology. Applications of information technology are arbitrarily segmented between approaches used to connect information and approaches to connect people.

Best practices to connect information call for the use of a services-oriented architecture. Services should interoperate through well-defined interfaces. The architecture defining the interface should include Enterprise, Information, Computational, and Engineering viewpoints, and be technology platform neutral. The information should be represented utilizing internationally accepted standards where available.

Communications using information technology is rapidly evolving. Tremendous opportunities exist in utilizing web technologies, especially the emerging Web 2.0 approaches to community organization and business.

### **Personalized Medicine Ecosystem as a Learning System.**

A key benefit of conceptualizing the complete Personalized Medicine ecosystem is the capacity to convert biomedicine into a learning system. More specifically, by capturing the entire biomedical life cycle, it is possible to synergistically combine research, care delivery, effectiveness measurement, quality assessment, and safety.

### **Cancer as the Pioneering Field in Personalized Medicine**

Cancer researchers have been at the leading edge of the Personalized Medicine revolution, and many of the first-generation personalized medicine products have been developed for cancer indications. There are three obvious reasons for this early focus:

- First, cancer is a complex set of diseases, for which molecular medicine approaches predate even the Human Genome Project. It has been known for decades that cancers are caused by genetic changes – either inherited or acquired – that result in abnormal cell proliferation, cell division or cell death.

- Second, cancer is a serious, often deadly condition, for which the efficacy rates of therapeutics have traditionally been extremely low. Since selection of the most efficacious treatment for the patient can be an urgent life-or-death decision, personalized medicine approaches vs. time-consuming “trial and error” are compelling.
- Third, the adverse effects of cancer therapeutics are extremely unpleasant, disfiguring and potentially fatal, thereby making it even more important to select the optimum therapeutic choice the first time, to avoid the doubly-negative impact of adverse effects from futile treatment.

### **The National Cancer Institute’s 21st Century Biomedical Test-bed The NCI’s Unique Research and Care Delivery Platforms.**

The NCI has a unique collection of administrative platforms that capture the entire lifecycle of biomedicine development, and hence it supports a unique environment in which the Personalized Medicine paradigm can be prototyped. For over 30 years, NCI has supported Comprehensive Cancer Centers, which blend research, care delivery, and prevention. There are more than 60 of these centers, distributed nationally and housed at the most prestigious research and care delivery institutions throughout the United States. More specialized programs include more than 50 NCI Specialized Programs of Research Excellence (SPORes) that support translational research, and 10 NCI Cooperative Group programs that conduct multi-institutional clinical trials. Most recently in the care delivery area, the NCI has launched a Community Cancer Center Program (NCCCCP) with 16 sites that cover 20 million lives.

## **II. The Cancer Biomedical Informatics Grid (caBIG®): Proof of Concept Platform for Personalized Medicine**

### **Origins and Development of caBIG®**

The National Cancer Institute (NCI) identified the need in 2003 for an informatics initiative of unprecedented scope for the biomedical community in recognition of three factors: the growing clinical and economic burden of cancer; the transformation of research catalyzed by the molecular revolution and multiple genomics technologies that were generating massive amounts of data; and the recognition that the “essential unity” of research and clinical care had powerful potential to improve the outcomes of all cancers, as it had done in the field of pediatric oncology.

As a first step in building an informatics infrastructure that would enable Personalized Medicine, the NCI officially launched the caBIG® (cancer Biomedical Informatics Grid) initiative in 2004 as a pilot program. Its initial objective was to develop capabilities that would meet the self-identified needs of the NCI Cancer Center community. (For more information on the history of caBIG®, see the [caBIG® Pilot Phase Report at http://cabig.cancer.gov/resources/report.asp](http://cabig.cancer.gov/resources/report.asp))

### **caBIG® Strategic Principles.**

Four fundamental principles underlie the activities of caBIG® and guide all of its operations:

- **Open Access:** Participation in caBIG® and the products delivered by caBIG® are open to all, enabling access to tools, data, and infrastructure by the cancer and greater biomedical research communities.

- **Open Development:** Software development projects are assigned to particular participants, but are informed iteratively with multiple opportunities for review, comment, further modification, and development by the caBIG® community.
- **Open Source:** The software code underlying caBIG® tools developed with the support of the NCI is available to software developers for use and modification. This software is licensed as open source to promote the reuse of existing code, hence optimizing the full benefit of the research dollars spent. Nonetheless, caBIG® recognizes the need for and importance of commercial software to the biomedical enterprise, and accommodates it through caBIG® interfaces. The open source license is industry-friendly, allowing commercialization of derivative products and fostering industry interest and innovation, while still adhering to the principle of open source for caBIG®-funded activities.
- **Federation:** caBIG® software and standards enable local organizations, such as Cancer Centers, to share data resources with the larger cancer care and research community and to use resources contributed by others. On the grid, these resources can be aggregated from multiple sites to appear as an integrated research dataset, while the individual resources remain under the control of the local organizations.

**caBIG® as the World Wide Web of Cancer Research.** caBIG® provides infrastructure for creating, communicating, and sharing bioinformatics tools, data, and research results, while using shared applications, shared data standards, and shared data models, all operating on a cancer community network (caGrid).

caGrid is underlying service oriented architecture that provides universal mechanisms for enabling interoperable programmatic access to data and analytics in caBIG®. caGrid also creates a self-described infrastructure wherein the structure and semantics of data can be programmatically determined, and provide a means by which services available in caBIG® can be programmatically discovered and leveraged.

There are to date over 100 grid nodes currently online at a variety of U.S. government, academic and commercial organizations, enabling those entities to share data.

### **Use-driven Capabilities – Real Solutions to Real Problems**

caBIG® provides more than 40 software tools, as well as the connecting network called caGrid, by which every function required in the molecular-based discovery and clinical research continuum can be performed and linked together.

The extensive and continually evolving portfolio of caBIG® capabilities can be reviewed at the website ([www.cabig.nci.nih.gov](http://www.cabig.nci.nih.gov)) and freely downloaded for use.

## **III. caBIG® Enterprise: Platform for Networking the Global Biomedical Community**

### **Unifying Research and Care**

Beyond providing the informatics needed for molecular based research, there is a need in Personalized Medicine to link the research endeavor back to health care delivery. Specifically, caBIG® is providing the ability to integrate molecular profiling, family history and molecular diagnostics into the Electronic Health Record, as well as to share back clinical outcomes data and clinical trial results into the discovery enterprise to achieve a ‘rapid learning’ system.

Following the completion of the pilot phase of the caBIG® initiative, the NCI took the next step towards an infrastructure for Personalized Medicine by extending caBIG® to an “enterprise phase”, with expanded capabilities to network the larger cancer community and beyond.

Today, caBIG® is a network of interconnected data, individuals, and organizations, designed to share data and knowledge, simplify collaboration, speed research to move new diagnostics and therapeutics from bench to bedside faster and more cost effectively, and ultimately to realize the potential of Personalized Medicine to improve patient outcomes.

A total of 56 NCI-designated Cancer Centers across the nation are working to connect their research and clinical care capabilities into a caBIG®-enabled information network. Through the NCI’s Community Cancer Centers Program (NCCCP), 16 Community Cancer Centers that in the aggregate touch 20 million lives are also becoming a part of this network. caBIG®-enabled connectivity enables these Centers to participate in clinical research studies and to bring the benefits of Personalized Medicine to their patient population in real time.

More than 1,000 individuals from over 200 organizations have participated in caBIG® activities since the initiative’s inception. Moving forward, however, it will be difficult to count the participants, since research users are increasingly applying caBIG® tools automatically as part of their studies without even noticing that they are “powered” by caBIG® infrastructure. In addition, as more and more software becomes caBIG®-compatible, countless users will benefit from its interoperability features without awareness of its presence.

### **caBIG® in Action**

In the “enterprise” phase, caBIG® infrastructure and tools are becoming ubiquitous among NCI intramural and extramural programs, as it enables and accelerates basic and clinical research. Representative examples of such caBIG®-enabled activities are:

**Inter-SPORE Prostate Biomarker Study (IPBS).** The SPORES (Specialized Programs of Research Excellence) are NCI-sponsored clinical research groups each specializing in a particular type of cancer. While each SPORE conducts its own trials, when biomarkers have been compared between centers, there has been a high degree of variability in the clinical significance of biomarkers screened from one center to another. The IPBS study was designed to assess ways to unify the data collection and analysis of samples, improving consistency of results. The IPBS study leverages caGrid to connect all participating centers, and applies caTissue to track the samples and manage the analysis results.

**caBIG™ and Mutational Analysis.** The International HapMap project is a continuing effort to compare the genetic sequences of groups of different individuals to identify chromosomal regions where genetic variants are shared. The first two phases were completed in 2007 and opened the door to wider use of Genome Wide Association Studies (GWAS), where DNA markers are scanned across the genomes of many individuals to find genetic variations associated with a particular disease. In the past year, GWAS studies have found genetic associations for coronary heart disease, Type I diabetes, and breast cancer, among others.

However, researchers need sophisticated tools in order to make sense of the potentially millions of data points generated in a single GWAS study. To make these studies both simpler to interpret and more productive to find disease associations, caBIG® has created several tools to analyze data from GWAS and other mutational studies. The cancer Genome-Wide Association Studies (caGWAS) model allows researchers to integrate, query, report, and analyze significant associations between genetic variations and disease, drug response or other clinical outcomes,

helping researchers to find the “needle in a haystack”. Originally developed for use in cancer research, the caGWAS model was extended to accommodate the specific study needs of the cardiovascular research community as well.

In addition, the Cancer Genetic Markers for Susceptibility (CGEMS) project represents the first public release of a GWAS study for cancer. Accessible by the CGEMS data portal (<http://cgems.cancer.gov>), over 500,000 SNPs have been analyzed so far, facilitated by caGWAS to produce and upload pre-computed results tables rapidly.

The data generated as part of the CGEMS program has already helped identify variations in FGFR2, associated with increased risk for breast cancer, and multiple loci associated with increased risk for prostate cancer.

**The Cancer Genome Atlas and the Cancer Molecular Analysis Portal.** One of the biggest challenges to researchers of high throughput genomics technologies is how to collect and work with the large quantities of diverse experimental data. The caBIG<sup>®</sup>-enabled Cancer Molecular Analysis (CMA) Portal (<http://cma.nci.nih.gov>) provides powerful tools and resources that enable cancer researchers across the world to explore, visualize, and integrate genomic characterization, sequencing, and clinical data from a variety of data sets.

The Portal exemplifies the caBIG<sup>®</sup> core principles of open development and federation. The CMA Portal allows researchers to use analysis programs developed at three different organizations, and to access data produced by more than 10 different institutions, all by a unified web interface. The tools available on CMA Portal allow researchers to access clinical characteristics such as survival data and tumor staging, and correlate those with mutation and other genomic data. This capability enables researchers to conduct cross-platform queries, helping them to find correlations between research and clinical data that would be difficult, if not impossible, to find using conventional means.

The first data set accessible from the CMA Portal is from The Cancer Genome Atlas (TCGA). TCGA is a comprehensive and coordinated effort to improve understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. TCGA is an integrative, multidisciplinary effort to develop and assess a framework for systematically identifying and characterizing the genomic changes associated with three cancer types: glioblastoma multiforme, squamous cell carcinoma of the lung, and serous cystadenocarcinoma of the ovary. Together, TCGA and CMA advance the opportunities for scientists and clinicians to analyze and employ TCGA data, to develop a new generation of targeted diagnostics, therapeutics, and preventives for cancer, and pave the way for more personalized cancer medicine.

**FIREBIRD.** To participate in FDA-sanctioned clinical trials, all investigators must fill out a variety of certification documents; key among them is the FDA registration Form 1572. Until recently these were paper-based forms, but the Federal Investigator Registry of Biomedical Informatics Research Data (FIREBIRD) application is changing that process. FIREBIRD is the first module implemented toward the vision for a Clinical Research Information Exchange (CRIX) infrastructure. FIREBIRD will leverage legally enforceable digital signatures compliant with Title 21 Regulations using an Identity Assurance infrastructure, Secure Access for Everyone (SAFE).

FIREBIRD enables investigators to register online with the National Cancer Institute and other sponsors, including medical product companies. Through a single web-based interface to a secure

central repository, investigators will be able to maintain their profile containing the accreditation information required for their participation in biologic, drug, or medical device trials. Investigators electing to participate in government, academic, or industry trials can access and apply their profile information to regulatory submission documents automatically, thus removing paper-based latencies and infrastructure costs. FIREBIRD is already in wide use across the clinical research community.

**National Lung Screening Trial.** Medical images play a critical role in cancer diagnosis and treatment, and the DICOM (Digital Imaging and Communications in Medicine) image standards allow technical interoperability between various medical imaging hardware and software systems. These standards, however, do not address workflow issues or how to integrate medical images with other types of biomedical information, such as genomic data, or clinical outcomes information. In addition, a standard part of the DICOM format includes the patient's name within the structure of the image file, complicating de-identification of the images for later population studies.

The caBIG® Imaging program has several collaborations underway:

- The National Lung Screening Trial uses caBIG® imaging tools to integrate radiology and pathology data.
- The Grid-enabled MAX project involves integration of caBIG® tools with all the current cooperative group quality assurance activities for imaging and radiation therapy from the Quality Assurance Review Center (QARC) and the University of Massachusetts Medical School and NCI Advanced Technology Consortium (ATC).
- An additional project expands the application of caBIG® imaging tools to optical images generated by digital histology imaging tools.

**I-SPY.** Unlike the treatments provided for most other diseases, cancer therapeutics are virtually all toxic compounds. To minimize the side effects and improve efficacy of these treatment with these agents, it is vital to identify biomarkers to predict which agents will be most effective for a particular cancer.

The I-SPY 1 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular analysis) trial is a national study to identify these biomarkers that may be predictive of response to therapy for women with late stage breast cancer.

Informatics support for the I-SPY trial includes integrating and analyzing clinical, MRI imaging, gene expression, CGH, Immunohistochemistry, and other data types. By correlating MRI image data with this collection of molecular characterization data from the tumors, researchers hope to identify biomarkers predictive for outcomes, ultimately resulting in more effective patient treatments. The integration for I-SPY comes from caIntegrator, providing data warehousing and data mining access to researchers via a web portal, and provides an excellent example of cross-study integration and analysis in support of translational research. Over 300 women with stage II and III breast cancer have been enrolled to date. The study has also established standards for MR imaging and developed novel tools for data sharing, tissue tracking, common information repositories and clinical trial automation.

The TRANSCEND project (TRANslational Informatics System to Coordinate Emerging Biomarkers, Novel Agents, and Clinical Data) is a follow-on to the I-SPY 1 trial. The goal of

TRANSCEND is to develop the next generation of clinical trials data collection by the use of web-based case-report forms (CRFs) to simplify data collection, improve collection of clinical data in support of the CRF forms at 2 I-SPY trial sites, demonstrate integration with an electronic health record system (Tolven eCHR) with the bioinformatics infrastructure in place for the I-SPY 1 trial, and develop common data elements (CDEs) for breast cancer. In addition to the caBIG<sup>®</sup> tools used in I-SPY 1, caTissue and NCIA are part of the informatics infrastructure being developed for TRANSCEND.

**Clinical Data Management System (CDMS).** An overarching goal of caBIG<sup>®</sup> is to increase collaboration between basic and clinical researchers by encouraging the adoption of standards-based tools and data collection. One area where the lack of standards seriously inhibits large-scale data comparison is in multisite clinical trials. This issue was recognized by the Clinical Trials Working Group of the National Cancer Advisory Board report “Restructuring the National Cancer Clinical Trials Enterprise”, which recommended creating an interoperable information technology platform for clinical trials. Broad use of standards-based electronic data capture systems improves the quality and comparability of data obtained at the different sites, facilitates multicenter trials, reduces trial administration overhead, and provides significant cost and time savings when compared with paper-based systems.

The NCI recently announced that it had acquired licensing rights from Medidata to distribute the Rave<sup>®</sup> Clinical Data Management System (CDMS) software package, with related installation, support, and maintenance services free to any interested NCI-funded organizations conducting oncology clinical trials. The new software will interoperate with other caBIG<sup>®</sup>-compatible software tools, and will enable data sharing and collaboration within each research organization, between diverse research organizations, and with NCI itself.

### **Beyond Cancer**

The tools and infrastructure of caBIG<sup>®</sup> can be generalized and applied in a variety of biomedical settings beyond the initial cancer community, as follows:

- *Beyond cancer*, the tools and infrastructure of caBIG<sup>®</sup> are being used to enable Personalized Medicine approaches in other therapeutic areas, such as in cardiovascular disease at the National Heart Lung and Blood Institute (NHLBI).
- *Beyond research*, caBIG<sup>®</sup> is linking discovery, clinical research and care delivery, in order to achieve the essential unity of research and care.
- *Beyond the National Institutes of Health*, caBIG<sup>®</sup> is being integrated into the federal health architecture to connect the Nationwide Health Information Network.
- *Beyond U.S. borders*, caBIG<sup>®</sup> tools and infrastructure are being adopted to enable biomedical enterprises in the United Kingdom, India, Singapore, China, and some countries in Latin America to achieve Personalized Medicine.
- *Beyond the “silos” of the traditional health care enterprise*, the caBIG<sup>®</sup> infrastructure is being applied to link a complex ecosystem of constituencies in the BIG Health Consortium (see Section IV below), to demonstrate Personalized Medicine in real settings, in real time.

## caBIG® Architecture and Health

Effective communication and collaboration between the clinical research and clinical care communities requires the use of common standards-based systems for data collection and management. Unfortunately, it is often *competing standards* rather than a *lack of standards* that inhibits interoperability between these communities.

To address this problem, the stakeholders from the Clinical Data Interchange Standards Consortium (CDISC), the HL7 Regulated Clinical Research Information Management Technical Committee (RCRIM TC), the National Cancer Institute (NCI), and the US Food and Drug Administration (FDA) have worked together to produce a shared view of the dynamic and static semantics that collectively define the domain of clinical and preclinical protocol-driven research, and the associated regulatory “metadata” that describes the clinical trial.

The caBIG® policies and tools that specify controlled terminologies, data element structure, data models, and computable metadata about those data elements are all openly developed, made freely available, and provide a pre-made framework for an effort like BRIDG. The caBIG® program has been a key partner and supporter of BRIDG and was instrumental in bringing the interested parties together at the outset. caBIG® continues to play a critical role in future plans to produce a similar data standards model for the non-clinical research space.

## IV. The BIG Health Consortium: 21<sup>st</sup> Century Model for Biomedicine

As the next step in its strategy to achieve Personalized Medicine, the NCI is pro-actively working to break down the traditional silos of the biomedical enterprise and work collaboratively with all the key stakeholders that must be empowered in this new paradigm.

On September 10, 2008, the NCI convened 25+ leaders from academe, government, advocacy, policy, and commerce, to grapple with the daunting challenge of transforming the biomedical enterprise to achieve the benefits of Personalized Medicine and demonstrate that the “disconnected islands” of the 20<sup>th</sup> century can be reconfigured to improve health care. A new group, known as the BIG Health Consortium, was formally launched that day.

### Mission and Goals

The BIG Health consortium is a partnership comprised of all the key stakeholders in health care: patients, providers, payers, product innovators, advocates, investors, and information technologists. Conceived by the National Cancer Institute (NCI), its mission is to show – in real settings, in real time – how and why personalized medicine works. Through a series of demonstration projects, BIG Health is modeling a new approach in which clinical care, clinical research, and scientific discovery are linked.

The goals of BIG Health are to:

- Demonstrate feasibility of implementing a new model of translational medicine
- Create an “ecosystem” of participants that seamlessly integrate research, care delivery and consumer health information
- Break down traditional silos that are barriers to rapid discovery and learnings
- Accelerate and enhance research productivity and improve clinical outcomes

### Assembling a New, Integrated Ecosystem

The BIG Health Consortium™ is designed to foster an integrated and interactive ecosystem (or “mega-community”) of previously unlinked sectors within life sciences and health care, who



gather to conduct demonstration projects to make Personalized Medicine a reality. Each participating organization is expected to share its capabilities, as well as to derive benefit, in order to have a self-sustaining endeavor.

Among the organizations that are participating in the BIG Health Consortium™ are cancer centers; integrated healthcare providers; academic centers; medical schools; diagnostic laboratories and product developers; personal genomics firms; patient advocacy and action-tank organizations; venture capitalists; biopharmaceutical companies; and government programs.

The informatics infrastructure of caBIG® will be generalized to “BIG” (Biomedical Informatics Grid) and applied as the underlying connectivity or “electronic glue” for BIG Health.

# **Coriell Institute for Medical Research**

## **Camden, New Jersey**

### **The Coriell Personalized Medicine Collaborative** *Examining the Utility of Genome-Informed Medicine*

**Michael F. Christman, Ph.D.**

*President and Chief Executive Officer, Coriell Institute for Medical Research*

#### **Executive Summary**

The Coriell Personalized Medicine Collaborative (CPMC) is a research study that employs an evidence-based approach to determine the utility of using personal genome information in health management and clinical decision-making. The CPMC also aims to build a cohort with rich genotypic and phenotypic data with which to discover genetic variants that affect drug toxicity and efficacy, as well as to discover presently unknown gene variants that elevate a person's risk of cancer and other complex diseases.

This forward-looking, collaborative effort involves physicians, scientists, ethicists, genetic counselors, volunteer study participants, and information technology experts. Its goal is to better understand the impact of personalized, or genome-informed, medicine and guide its ethical, legal and responsible implementation. The study will enroll 10,000 individuals by the end of 2009 with an ultimate goal of 100,000 participants. As of October 2008, there were 3,000 participants enrolled in the study. There is no charge to study participants.

#### **Challenges of Implementing Personalized Medicine**

Genome-informed medicine is the use of an individual's genetic information to predict disease, avoid adverse drug reactions and tailor treatment<sup>1-3</sup>. The successful implementation of personalized medicine is dependent upon several factors. First, there is a critical need to educate health professionals<sup>4-7</sup>. The amount of genetics traditionally taught in medical schools is limited and typically focused on single-gene disorders and chromosome abnormalities, with little exposure of students to complex genetics. Second, the implementation of personalized medicine requires government support and regulatory oversight<sup>8-10</sup>, as well as public vetting of ethical issues<sup>11, 12</sup>. Third, medical records systems must be structured to accept genetic data and integrate them with the patient's existing health record in a way that facilitates its use in clinical decision-making.

Additional challenges to evidence-based research into the effectiveness of personalized medicine include the need for large cohorts and longitudinal data collection to generate sufficient data to compute the treatment effect and gauge the potential costs and benefits. Cohort size must be large enough to address 1) genetic variants of low frequency (~1 to 2 percent), 2) gene-environment effects, 3) gene-gene interactions, and 4) loss of

participants to follow-up. There are also consent and privacy issues that come into play in large cohort studies <sup>13</sup>. In addition, genetic studies of large cohorts require significant biobanking, genotyping and information technology infrastructure <sup>14</sup>.

### **The Importance of Biobanking**

The mission of the Coriell Institute includes the collection, characterization, storage, and distribution of valuable biomaterials and associated data for scientific research. Coriell has more than forty years experience in developing and maintaining biorepositories as national and international resources for the study of human diseases and aging. The Institute continues to expand its information management systems to meet evolving business and scientific requirements. Coriell has a state-of-the-art laboratory and data management system and a web-based catalog for biomaterials and associated data.

Since the inception of the Coriell Cell Repositories, more than 150,000 cell cultures have been distributed to investigators in laboratories in the United States and sixty-two foreign countries. More than 500,000 aliquots of DNA have been shipped from all Coriell-managed repositories to investigators throughout the world. Coriell's Repository Information Management System was designed to facilitate and streamline high-volume biomaterials and data distribution management. Coriell has been managing web-based access to genome-wide genotype data on hundreds of samples in its collections during the past several years. Its biorepository capabilities include significant phenotypic data management, with use of standardized phenotypic language and collection of longitudinal data for its disease collections <sup>15, 16</sup>. Additionally, Coriell has partnered with several regional healthcare systems that are rapidly moving toward comprehensive electronic medical record systems. These assets position Coriell and its partners to meet the challenges of translating genomics into clinical practice.

### **Need for Evidence-Based Research Studies**

The Human Genome Project <sup>17</sup>, the SNP Consortium <sup>18</sup> and the HapMap Project <sup>19</sup> have served to lay the foundation for the next generation of efforts to map complex disease genes and the quantitative trait loci (QTLs) <sup>20</sup> that may be preclinical indicators of pending disease. To make this information useful in improving health and the quality of life, the mechanism for sharing genetic variation information associated with complex diseases with individuals and healthcare providers must be constructed, and evidence-based studies must be performed to assess the outcomes from receipt and utilization of this information. These are the major goals of Coriell's research study.

The importance and need for an evidence-based initiative has not gone unrecognized by others in the scientific community. Dr. Francis Collins, former National Human Genome Research Institute director and human genome project pioneer, stated in a June 6, 2008 interview with Science magazine, "We desperately need, in this country, a large-scale, prospective, population-based cohort study. And we need to enroll at a minimum half a million people. We would need to have their environmental exposures carefully monitored and recorded, their DNA information recorded, their electronic medical records included, and have them consented for all sorts of other follow-ups." The cost to perform such a study has been estimated at 300 to 400 million dollars per year. Coriell's CPMC study has been constructed such that participants may opt to share their

anonymized genotypic and phenotypic data with the scientific community, where it can be combined with other datasets in large genome-wide association studies.

### **The Coriell Approach**

The CPMC aims to be a model for the ethical, legal and responsible implementation of genome-informed personalized medicine. The CPMC study is structured to allow dynamic communications between Coriell and study participants using a secure web portal. Web-based surveys will be used to assess health and behavioral outcomes related to the personal genetic variant information released by the study. Additionally, this portal will allow participants to share their data with healthcare professionals. Currently, the CPMC is funded through philanthropic donors and institutional support, with no cost to individual study participants. An outline of the CPMC research study is shown below (Figure 1).

After participants have given their informed consent, they are asked to donate two milliliters of saliva for genome profiling using a microarray platform (Affymetrix 6.0 Genechip, Affymetrix, Santa Clara, CA) and targeted SNP profiling using a bead-based platform (Illumina BeadXpress, Illumina, San Diego, CA). An outside panel termed the “Informed Cohort Oversight Board” (ICOB) meets at least twice per year to review genetic variants, submitted by Coriell, as risk variants for health conditions. Only genetic variants associated with health conditions considered to be potentially medically actionable (i.e., where there is the potential to mitigate risk, and those variants for which a significant association has been replicated) are then returned to participants via a secure web portal. Participants are able to grant access to their physician(s) to view the results and may request to discuss their results with a CPMC genetic counselor at no cost. A variety of outcome measures are assessed via web-based surveys completed by participants regarding their actions, physician actions, attitudes and, ultimately, health outcomes. Participants are asked to update their medical, family and lifestyle information annually such that longitudinal datasets are generated. Thus, there are several dynamic aspects of the CPMC, including ongoing review of association studies to identify variants for submission to the ICOB, continual outcomes research and the longitudinal collection of participant medical records on an annual basis.



**Figure 1.** Outline of the CPMC Research Study

The CPMC research study involves (1) informed consent and saliva collection; (2) genotyping; (3) viewing of genetic results; (4) optional sharing of genetic results; and (5) outcomes research.

### **Engagement of Hospital Partners and Medical Professionals**

With respect to the challenge of integrating genomic information into the practice of medicine, the education of medical professionals, particularly doctors and nurses, is likely to be a rate-limiting step. Coriell understands the importance of engaging clinicians and other medical professionals to develop successful strategies for integrating complex genetic information into the current medical paradigm, and does so by engaging these individuals in the CPMC both as collaborators and participants. In addition, Coriell appreciates the commonality of cancer in society and the enormous potential for cancer research and cancer care to be impacted by personalized medicine. Thus, Coriell has established collaborations with neighboring healthcare partners for the CPMC study.

Coriell established a partnership with next-door neighbor and tertiary teaching hospital, Cooper University Hospital, in March 2008. Cooper University Hospital is the clinical campus for the Robert Wood Johnson Medical School of the University of Medicine and Dentistry of New Jersey and has more than 550 physicians in more than seventy-five subspecialties. In July 2008, Coriell announced its collaboration with community-based Virtua Health. The collaboration with Virtua was born out of the understanding that most of the population is treated in community health centers, as opposed to academic medical

centers, which are often located in urban areas. Virtua is a community health system with four hospitals, numerous outpatient centers and more than 1,800 physicians in its network. Coriell also formed a collaborative relationship with Fox Chase Cancer Center, one of thirty-nine National Cancer Institute-designated comprehensive cancer centers and a center with a long tradition of excellence in combining state-of-the-art patient care with cutting-edge genetic research. In addition, a number of other partnerships with the CPMC are being discussed. Coriell encourages the enrollment of medical professionals and health center employees into the research study. These ties energize the study and open the door to educate medical professionals about genomics.

One of the strategies to educate medical professionals will involve seminars given by Coriell scientists and hospital partner physicians. Coriell is developing a seminar series on genomic medicine in collaboration with partner hospitals. Seminars will focus on diseases included in the CPMC and will meet the requirements of Continuing Medical Education (CME) such that attendees may gain CME credits. In an attempt to make education as accessible to healthcare providers as possible, Coriell may post the genomic medicine seminars online as webcasts.

Coriell will also look to medical professionals for input to ensure effective mechanisms are developed for using genomic data in the clinical setting. Questions to be addressed include:

- How is genome information best conveyed in the typical twelve-minute office visit?
- What type of information do healthcare providers want to see in a genome-wide genetic test report and in what context?
- What resources and tools are needed by healthcare providers to appropriately use genome information and educate their patients?

Realization of genomic medicine will require a two-way exchange in which scientists educate medical professionals and vice versa. This exchange will involve traditional communication in addition to that of medical and genetic datasets (in the form of electronic medical records and large numbers of genetic test results, respectively). Coriell expects that the deep engagement of several hospitals partners in the CPMC will catalyze this dialogue. Moreover, it is anticipated that as CPMC participants invite their healthcare providers to view their personal genetic results, Coriell will have an engaged and accessible population of healthcare providers to whom targeted surveys may be directed regarding use of genome information in medical care.

### **Recruitment of CPMC Study Participants**

Recruitment of individuals into the CPMC is primarily conducted during informed consent sessions held at the Coriell Institute, partner hospitals or other community locations. The principal investigator of the CPMC, or a CPMC scientist, discusses the details of the study, possible risks, the content of the Informed Consent document, and provides attendees with the opportunity to ask questions. Upon signing of the Informed Consent document, newly enrolled individuals are invited to submit a small saliva sample.

Eligibility requirements are limited to requiring that participants are eighteen years old and older, have a valid email address and are willing to complete web-based surveys throughout the course of several years. Participants may opt (at the time of enrollment or any time thereafter via the secure web portal) to release their anonymized genome-wide variant data and medical history data to the scientific community for association studies. There is no charge to participants in the CPMC study.

### **CPMC's Cancer Arm**

Coriell's partnership with healthcare centers including Fox Chase Cancer Center enables the study to have a cancer arm in addition to the wellness arm described above. Among the first 10,000 participants, the goal is to enroll 2,500 patients with breast cancer and 2,500 patients with prostate cancer. There is evidence that the baseline risk to develop cancer is strongly influenced by genetic variation and that in cancer patients, the response to chemotherapeutic agents, adverse events from medication and clinical outcomes are influenced by a patient's genetic makeup. Thus, the creation of a large cohort of breast and prostate cancer patients with rich phenotypic datasets from the national cancer registries, as well as genome-wide genetic information, will allow researchers to examine the role of genetic variants in pharmacogenomic and clinical endpoints. For those participants who agree to allow the CPMC to share their anonymized data, such data will be made available to the larger scientific community through the National Center for Biotechnology Information (NCBI) database of Genotype and Phenotype (dbGaP) resource.

### **Clinical Laboratory Improvement Act (CLIA) Compliance**

The CPMC's goal to examine the potential use of genome information in clinical practice requires that the testing be performed in a Clinical Laboratory Improvement Act (CLIA)-approved laboratory. Therefore, the Coriell Genotyping and Microarray Center applied for and obtained CLIA certification to perform genotyping assays using the Affymetrix GeneChip platform. Soon, Coriell will expand its initial application to include CLIA certification for genotyping using the Illumina BeadExpress platform.

### **Powerful Analysis: Coriell Genotyping and Microarray Center**

The Coriell Genotyping and Microarray Center uses the Affymetrix Genome-Wide Human SNP Array 6.0. The Affymetrix array was designed to provide broad coverage of SNPs across the entire genome through genotyping at more than 900,000 SNPs. Due to this design, SNPs known to have an association with a particular phenotype may not be present on the chip or represented through a perfect proxy SNP. To compensate, Coriell will use custom-designed SNP panels to include the disease-relevant SNPs absent from the Affymetrix platform. These panels will be analyzed on the Illumina BeadExpress platform.

### **Regulatory Body: Informed Cohort Oversight Board**

The purpose of the Informed Cohort Oversight Board (ICOB) is to evaluate the medical actionability of health conditions and the evidence of a genetic risk variant's potential medical "actionability" with regard to this health condition. A major prerequisite for consideration of genetic variants is the validity of association studies in the published literature that suggest a significant association between genetic variants and specific

medical conditions. The ICOB thereby determines what personal genetic variant information will be returned to study participants. Approval is given when knowledge of a participant's status for a particular genetic variant has the potential to affect a healthcare provider's treatment course or permit the provider to offer advice about the participant's health or lifestyle that has the potential to mitigate risk. Using prospective, web-based outcomes surveys, the CPMC study will determine whether or not the use of variant information does indeed mitigate risk.

This external advisory board comprises highly esteemed scientists, healthcare professionals, an ethicist, and a community pastor. The concept of such a board was proposed by Dr. Kohane and colleagues<sup>21</sup>. This approach provides a model for a national system for evaluation of genome-informed medicine.

CPMC scientists review medical and scientific literature to identify candidate gene variants and provide summary reports to the ICOB. The ICOB reviews each report and votes to approve, disapprove or to request more information on each variant and condition. Factors to be considered include:

- Recommendations by the US Food and Drug Administration, Centers for Disease Control and Prevention, National Institutes of Health, National Associations for Medical Subspecialties, or other governmental advisory bodies.
- Seriousness of the disease, condition or potential adverse drug response.
- Number, size and quality of studies demonstrating a statistically significant association of a gene variant with the condition. Meta- analyses, when available, are reviewed.
- Magnitude of the effect of the particular genetic variant.
- The risks and benefits of clinical or lifestyle intervention(s) to minimize or reduce the risk.
- Data elements to measure outcomes.

Approval by the ICOB means that the association between the genetic variant and the condition has been validated and that the condition is considered to be potentially medically actionable. Approval does not require that there be clear evidence that the variant has utility in affecting health outcomes. The goal of the CPMC is to provide the outcomes data to determine the utility of each genetic variant.

The ICOB meets at least twice per year. This frequency allows the study to integrate findings from peer-reviewed association studies for new associations and validations of prior findings. It is likely that over time, the CPMC will request the ICOB to re-review both previously rejected variants for which there is new scientific evidence and previously rejected health conditions for which prevention or treatment options have changed the potential actionability. ICOB decisions are determined by a majority vote. The group deliberations are conducted in private, assuring that scientific issues are debated in an objective, critical and unencumbered environment. However, the outcome of all deliberations is publicly disclosed through the web portal.



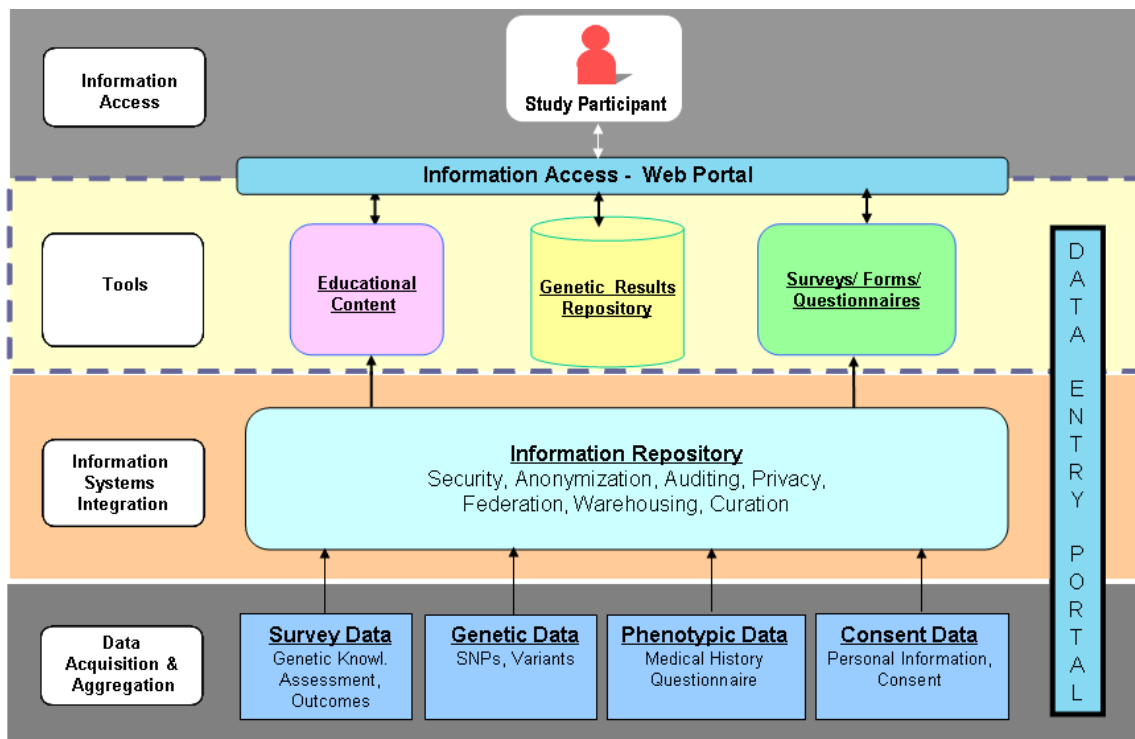
### **Dynamic Participant Engagement: Results Viewed Through Secure Web Portal**

The CPMC web portal is a website with several functions. It allows for 1) data collection through online surveys, 2) genetic variant results reporting, 3) education of participants and medical professionals, 4) secure sharing of personal genetic variant information with healthcare professionals, 5) web-based requests for access to data from scientists, and 6) web-based requests for genetic counseling from participants. It is a public site with a portal for participants to log in to a secure server. In the secure portion of the site, participants may set up their CPMC account with a password, change their contact information (email address), update their consent options (e.g., opt to release their anonymized data for genome-wide association studies (GWAS)), and view their personal genetic variant information as it is released.

Additionally, the CPMC web portal has a significant amount of genetic education material. This material is written for two distinct audiences, the lay participant and the medical professional, although any individual may access the more advanced educational material if desired. The educational pages include information on basic genetics and scientific milestones such as the Human Genomic Project and HapMap project. Educational material is also provided on inheritance, cancer, the multifactorial nature of complex disease, the meaning of “risk” and how to interpret disease risk assessments, and reasons why this type of study is only possible today.

With each visit to the web portal, participants are re-engaged. Participants must elect to view each genetic variant result independently, assuring that control over the results lies with the participant and that participants are not informed of results that they are not actively seeking. Individuals who choose to view CPMC results will watch a short educational video of a genetic counselor giving anticipatory guidance for that specific variant prior to viewing their personal genetic variant information. The CPMC encourages study participants to invite their healthcare providers to view their results. Participants may authorize access to their results directly from their CPMC web portal account.

In addition, the site has current information about opportunities available to participants such as no-cost genetic counseling, educational forums and additional surveys related to the study. There will be the potential for the CPMC to post information about other studies for which participants may be eligible. Figure 2 provides a diagram of the information system architecture for the study.



**Figure 2.** CPMC Study Information Architecture

Important to the maintenance of participant privacy is the fact that all personally identifying information is both encrypted and stored separately from genotype and medical information. Two-factor security is used to dynamically build the web pages as participants view their personal data.

**Realistic Risks: Explanations of the Magnitude of Risk Elevation**

The CPMC is committed to reporting realistic risks associated with genetic associations in a format that is understandable by the lay population. All results presented will illustrate the known population disease risk (specific to racial/sex/age groups, if known) and the adjusted risk based on the genetic variant genotype. Although in some cases a particular genotype may increase the risk significantly, it is expected that most genetic variants associated with complex (multifactorial) diseases will increase the risk only modestly. Until validated algorithms are available to combine risks associated with more than one genetic variant, each will be reported individually. References to the primary literature are included on all result reports.

To ensure that participants and healthcare providers understand the risks conferred by the genetic variants included in the CPMC results, an educational section of the web portal called “Understanding the Odds” has been created. This section, written for both lay and medical professional audiences, describes the concept that the risk of complex diseases is dynamic and involves the interaction of genes with the environment. Additionally, the genetic contribution toward a complex disease is discussed, addressing the likelihood that tens of individual genes, not a single variant whose current results are being reported and viewed, influence the genetic risk of complex disease. It is also explained that given the

current state of knowledge, family history is likely to be a larger risk factor for most complex diseases than any one genetic variant.

Coriell is using an additional tool to educate CPMC participants. Study participants will be invited to attend educational forums hosted by CPMC genetic counselors and clinicians from hospital partners. Upcoming events are announced to study participants through the CPMC web portal. The purpose of the forums is to educate participants about health conditions for which genetic variant information has been released as part of the CPMC study. At these sessions, the clinician will discuss the health condition, its causes (genetic and non-genetic), screening, treatment, and prevention strategies. The CPMC genetic counselor will discuss the genetic variants that are part of the CPMC study and their association with the condition, as well as the risk assessment supplied with the genetic information.

### **Understanding Results: Genetic Counseling**

Genetic counseling in the era of genomics and personalized medicine will require a new approach from traditional counseling for single-gene disorders<sup>22</sup>. Coriell employs full-time, board-certified genetic counselors who are dedicated to the CPMC study and available to provide genetic counseling to participants via email, phone and face-to-face office consultation, as well as through educational forums open to CPMC participants. Medical professionals whose patients are participating in the study may also request access to CPMC genetic counselors to discuss the study and the reported genetic variant information.

The genetic counselors will record all encounters with CPMC participants in a secure, password-protected tracking database that is only accessible to the CPMC genetic counselors. This database will allow the genetic counselors to have easy access to the history of contact between themselves and a participant. It will allow genetic counselors to track the amount of time and type of consults being made and to gather statistics on the types of diseases and variants for which the consults are being requested. This tracking system will also allow the genetic counselors to identify common areas of confusion around which future educational sessions for both the lay public and medical professionals can be tailored.

### **Medical History, Family History, and Lifestyle Questionnaires**

Participants are required to complete extensive medical history, family history and lifestyle questionnaires online after establishing their personal, online CPMC account. These surveys must be completed prior to viewing genetic results. Participants will be asked to update their medical history, family history and lifestyle information one year after the information is entered and every twelve months thereafter. These data will be used for two purposes: 1) they will be used in combination with genotype data to calculate personalized risk, whenever possible, and 2) they will be used in combination with genotype data in GWAS studies to identify additional genetic variants which contribute to complex disease and/or drug metabolism (for those participants who opted to allow their anonymized data to be used for association studies).

Coriell recognizes the importance of CPMC data in GWAS studies and has created a mechanism (via the participant consent form) for participants to indicate their willingness for their anonymized data to be shared with researchers (both from non-profit and for-profit organizations). As such, anonymized data from the CPMC will be available to all qualified researchers through the NCBI dbGaP web portal. The model is to perform surveys through the web portal, allowing cross-validation of data across questionnaires. The longitudinal nature of this project, the on-going release of genetic variant results, and the request for annual updates of survey information will allow for the collection of data that are traditionally hard to acquire, such as diet and exercise patterns over time and environmental exposures as they happen.

### **Longitudinal Data Collection: Electronic Medical Records**

Participants may opt to release recent medical records from their primary care healthcare provider via hard copy, or in electronic form if they are in a hospital partner's Electronic Medical Records (EMR) system. Updated medical records will be requested annually to ensure longitudinal data collection. These datasets will be monitored for changes in health outcomes relevant to conditions for which the CPMC has released genetic variant information. Medical records will be compared to self-reported patient medical history reports.

CPMC staff will transcribe a subset of the information in the medical record into a Personally Controlled Health Record for each participant. All Coriell information technology systems will allow compliance with established standards for interoperability (HL7) and medical data definitions such as SNOMED and LOINC.

### **Participant Privacy and Security**

Coriell has several provisions in place to maintain integrity, confidentiality and security of its data and information systems. Coriell has security policies in place to assure that all data are protected from unauthorized access, and maintains audit trails, backup procedures and error checking to assure accuracy and protection of CPMC data. Data security is a balanced combination of management and staff actions, operational activities and technological control measures. The CPMC information technology infrastructure requires three highly integrated technology layers: 1) web portal, 2) laboratory information management system for inventory management, phenotypic data management and process management, and 3) secure hardware infrastructure that contains web application servers, database servers, a storage array network, and network security appliances. Personally identifying information is encrypted and stored in a separate database from the genotype and medical data. Participants will also be required to log in to the secure web portal using their barcode identifier, username and a strong password.

### **Outreach to Minority Populations**

As the population of participant volunteers in the CPMC grows, Coriell is dedicated to ensuring that the genetic data collected are representative of the ethnic composition of the region. Camden, NJ, the community in which the Coriell Institute is located, is one of the poorest urban communities in the country, primarily made up of African-American and

Hispanic residents. Coriell's aim is to develop mechanisms to reach these historically underserved communities.

Coriell has enlisted the support of several groups to aid in minority recruitment. First, Coriell approached the religious community in Camden County, NJ. Second, prominent leaders are taking part in the study and offering their infrastructure to the project. Within the Hispanic and Latino community, Coriell has engaged local Hispanic political leaders including United States Senator Robert Menendez (D-NJ), Co-sponsor of S.976, "Genomics and Personalized Medicine Act of 2007." Finally, Coriell hosts enrollment events in Spanish and offers a Spanish version of the CPMC Informed Consent document.

### **Availability of CPMC Data to Researchers Worldwide**

The CPMC team has discussed with National Human Genome Research Institute a strategy for hosting anonymized data from CPMC participants that opt to share their data with scientists for research through the dbGaP web portal. Coriell is committed to ensuring widespread access to this valuable dataset. The Institute has a history of posting data with dbGaP for use by qualified scientists and has been involved in the return of genotypic data generated from samples in the Framingham Heart Study, as well as in the National Institutes of Neurologic Diseases and Stroke and the National Institute of General Medical Sciences repositories at Coriell.

### **Outcomes Research**

Follow-up studies of the actions of CPMC participants and healthcare providers, as well as participant health outcomes, are at the heart of this evidence-based study. A thorough assessment of medical history, family history and lifestyle at baseline is made prior to the release of personal genetic variant results. In addition, participants will be able to take part in other assessments, such as an examination of baseline knowledge of genetics.

When scaled appropriately, the data collected from the CPMC will be used to assess whether healthcare costs increase as a result of genome-informed medicine using objective criteria such as number of physician visits, tests ordered, data related to hospital admission, and drug prescriptions. Measures of physician practice based on surveys of physician beliefs and recommended practices will be balanced by examining choices made by participants in selection of healthcare options. Coriell will work with hospital partners to develop such metrics and with organizations such as the Technology Evaluation Center to ensure appropriate clinical data elements are monitored.

### **Summary**

The CPMC is an evidence-based research study designed to determine which elements of personal genetic data are valuable in clinical decision-making and healthcare outcomes. Medical records and genomic data will be updated dynamically. There is no charge to CPMC participants and, for participants who choose to release their data, anonymized genotypic and phenotypic data will be made available to qualified scientists. The CPMC will enroll 10,000 participants by the end of 2009 into wellness and cancer arms. Close partnerships with area hospitals are designed to catalyze physician engagement in personalized medicine.

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# **Harvard-Partners** Boston, Massachusetts

## **AN INFORMATION TECHNOLOGY INFRASTRUCTURE FOR BRINGING GENETICS TO MEDICINE**

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### ***Abstract***

The Harvard Medical School-Partners HealthCare Center for Genetics and Genomics (HPCGG) was founded in 2001 to develop and implement strategies for the incorporation of genetic/genomic information and knowledge into clinical medicine (“personalized medicine”) with the belief that such incorporation has the potential to change clinical outcomes and radically improve medical practice. As a part of this effort HPCGG was charged with enhancing the Partners HealthCare Systems (PHS) clinical enterprise infrastructure in a manner that would both speed the adoption and improve the quality of personalized medicine. To this end, HPCGG created facilities capable of incorporating new genetic and genomic instruments as they are developed. In addition to supporting research activities, these facilities support the HPCGG’s CLIA certified molecular diagnostic laboratory that is called the Laboratory for Molecular Medicine (LMM). The LMM offers gene based tests to clinicians for use in routine clinical care. Together with the PHS hospitals, these facilities and the LMM form an integrated healthcare delivery network capable of developing and offering molecular diagnostic tests and leveraging such knowledge to improve healthcare.

Early in the HPCGG’s development it became clear that substantial information technology (IT) investments would be required to enable personalized medicine to reach its potential. Five years ago a partnership between the HPCGG, the Partners HealthCare Information Systems Department and Hewlett Packard Corporation was formed to begin building the required infrastructure. This paper will describe the IT functionality that has been deployed to support and link together the HPCGG’s facilities, the LMM and the Partners HealthCare Electronic Health Record (EHR). We will also describe projects underway to further enhance our genetics/genomics based IT capabilities. In particular, we have identified two areas where new inter-institutional networks will be needed to prepare for wider adoption of genetic and genomic techniques in medicine. We will describe infrastructure we have begun to construct that might enable the establishment of these networks.

### ***The Nature of Genetic Based Diagnostic Tests***

Molecular diagnostics, also known as genetic or genomic based diagnostics, provide the bridge that enables physicians to bring genetic knowledge to routine patient care. Physicians use the information these tests generate for assessing disease risk, for



diagnosis, for prognosis and for making specific treatment decisions. The revolutionary effect these technologies will have on the health care system is already being felt: genetic tests are being used to guide treatment in clinical domains as diverse as heart disease, cancer, infectious disease, and many other common illnesses. At our Center we offer molecular diagnostics in different medical areas. These include cancer, cardiovascular disease, pharmacogenetics, pharmacogenomics, several childhood disorders and sensory neural disorders. Some tests are relatively simple in which the laboratory tests for a few genetic variants and others very complex where tens of kilobases of DNA are examined for variants and mutants. Specific examples include:

- Hypertrophic Cardiomyopathy that may result from mutations in any one of eleven different genes and is severe enough to result in sudden death if left untreated, and to assess the risk of their relatives for these disorders.
- Identify whether a patient's hearing loss is caused by genetic variants that are also correlated with other serious medical conditions.
- Determine whether non-small cell lung cancers have genetic variants that correlate with either Tyrosine Kinase Inhibitor (TKI) efficacy or resistance.
- Identify whether a patient has genetic variations that will cause him or her to metabolize Warfarin abnormally, either quickly (risking stroke) or slowly (risking brain hemorrhage).

The field of clinical molecular diagnostic testing is evolving quickly. A few years ago, nearly all genetic tests were gene-based tests that involved examining a small number of specific base pairs in a patient's DNA to determine whether particular mutations or variants were present. Today, we commonly run sequencing tests that read long segments of patient DNA in one gene or many genes and determine all the variations present in those sequences. There are many different technologies for DNA sequencing including Affymetrix resequencing Chip-based technologies that we have implemented in our Center. This technology has made it possible to survey increasingly large segments of DNA in a cost-effective manner. Newer sequencing technologies that promise even higher throughput and lower cost are ready to be implemented. Several national governments are funding research and many commercial entities are investing significant capital to reduce the cost of sequencing a person's entire genome to approximately \$1,000.

While we are at least a few years away from reaching this goal, new technologies will continue to drive down the cost of sequencing to costs that may be even less than \$1,000/genome.

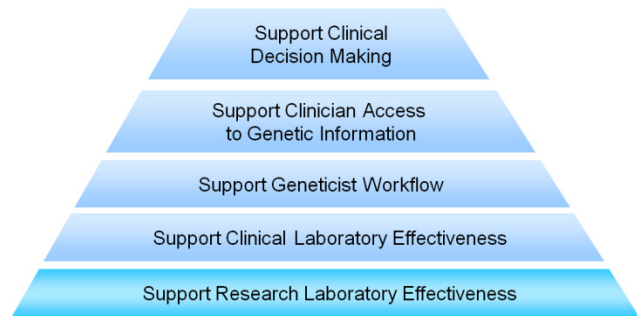
The continuous reduction in DNA sequencing costs will significantly affect how genetics is leveraged in the clinic. At present the cost of DNA sequencing is a barrier to increased use of molecular diagnostic testing. As this barrier is reduced, we believe the amount of patient DNA being sequenced will increase. We expect the number of variants identified in the patient population to grow continuously until it becomes feasible to cost effectively sequence all of the nearly 3 billion base pairs of a patient's genome. Current estimates place the number of variants that such a test would yield at 4-5 million per person. (Levy et al. 2007) The data generated by such a whole genome sequencing test would be good

for a person's lifetime. Sequencing would only need to be redone in the case of cancer or other disorders where somatic changes are important and for infectious agents.

We are rapidly approaching the day where we will be able to determine the precise DNA variations present in each patient. However, the process of determining the implications of each of these variants, let alone the implications of each combination of variants, will take longer. Our knowledge of the impact of genetic variation is constantly expanding and this knowledge expansion is likely to continue for many years to come. Ideally, clinicians would take into account the most up to date discoveries on every variant discovered in each patient as they prescribe care, but doing so is clearly beyond the capacity of the human mind. To reach this goal, clinicians will require far more extensive IT infrastructure than that exists today.

The rate of progress in technologies to accomplish the goal of sequencing the entire human genome is much greater than the rate at which progress is being made to provide IT support for such efforts. Clinicians will likely encounter

substantial challenges well before whole genome sequencing becomes routine. Present day chip based genotyping technologies are already capable of generating datasets that would overwhelm existing clinical knowledge management systems. For the past five years the Harvard Partners Center for Genetics and Genomics, the Partners HealthCare Information Systems department, and Hewlett Packard have been developing components of the IT infrastructure needed to address these issues. The applications we have built are supporting the use of genetics in the clinical environment; however, much work remains to be done to provide the depth of support clinicians will ultimately need.



**Figure 1: The process we have employed to stand up IT support for the use of Genetics in Medicine**

### ***The Partners HealthCare Genetics IT Infrastructure***

To be truly effective, IT infrastructure that helps manage genetic information must integrate laboratories, genetic professionals, the Electronic Health Record (EHR) and automated clinical decision support engines. Infrastructure of this scope must be built incrementally. In our institution, we began by constructing a platform to support the laboratories that generate genetic and genomic data. Next we built infrastructure that supports professional genetic experts and other healthcare professionals including genetic counselors. Then we integrated this infrastructure with the Partners HealthCare EHR. Finally we began the work of creating genetics based clinical decision support (CDS) functionality. We are now deepening our support for genetics in the EHR to enable broader genetics based clinical decision support. (Figure 1) As we do this, we are encountering challenges that cannot be solved by an individual organization acting independently. Therefore, we are working to establish networked infrastructure that will be needed to fully support personalized medicine.

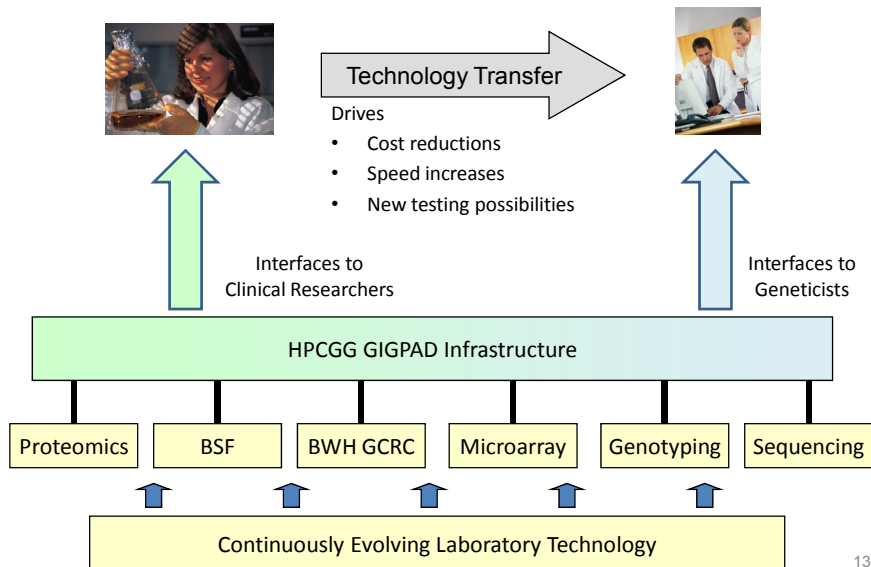
### ***Supporting the Laboratory: The Gateway for Genomics-Proteomics Applications and Data (GIGPAD)***

Almost all genetic and genomic data are generated in laboratories by complex machinery. Laboratory Information Management Systems (LIMS) are critical to an overall genomics IT infrastructure because they can help with workflow issues as well as capture genetic and genomic data in structured form when it is initially generated. Downstream bioinformatics, report generation, and clinical decision support systems depend on this structured genetic and genomic data. LIMS are also important for ensuring data integrity across the inter-organizational process flows associated with genetic testing. For these reasons, integrated LIMS support is an essential part of a genomic IT enterprise architecture. In addition, LIMS can help reduce costs and increase quality through process automation, reducing errors, facilitating communication and reducing the need for manual entry of information.

A large number of genetic and genomic technologies are used in research and they will migrate to clinical use. Maintaining multiple LIMS within an enterprise is both challenging and expensive. We have found that creating an Enterprise LIMS Superstructure can help address these problems. We created a system called the Gateway for Integrated-Genomic Proteomic Applications and Data (GIGPAD) to serve this function. GIGPAD serves as an umbrella over the individual LIMS in the environment and integrates them together. The system exposes unified user and system interfaces to the rest of the enterprise.

GIGPAD's umbrella style architecture (Figure 2) serves two purposes. First, it enables us to develop common functionality that can be shared across facilities. Order entry, accessioning, results return, the financial interface, user authentication and authorization functionality are all shared across facilities. Low volume facilities can leverage the umbrella layer to provide the required IT support. Higher volume facilities tend to need specialized LIMS functionality to assist in their workflow and integrate their instruments. We make individual laboratory build versus buy decisions for this type of specialized LIMS functionality. When we choose to buy, we integrate the purchased LIMS under the GIGPAD umbrella. The scope of these build or buy projects is smaller because of the common functionality contained in the umbrella layer.

## GIGPAD Architecture



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**Figure 2: GIGPAD is architected to enable reuse of functionality across the clinical and research environments.**

BSF, Biosample services facility; BWH GCRC, Brigham and Women's Hospital General Clinical Research Center

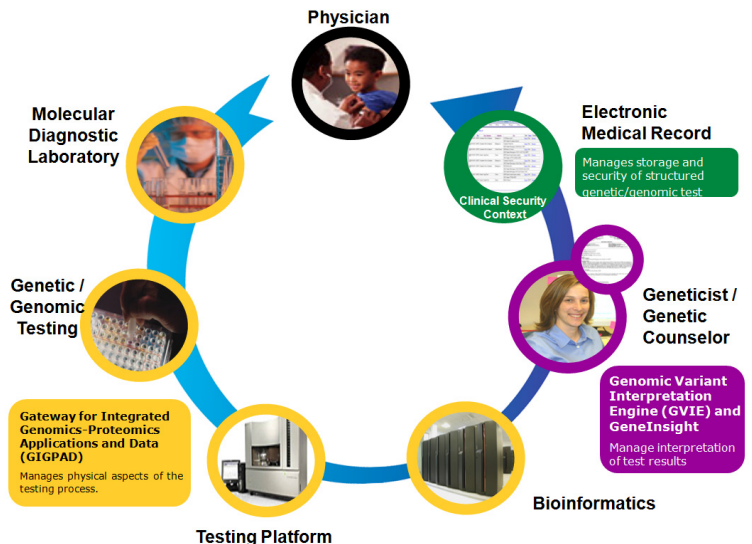
Second, we have enhanced the GIGPAD umbrella to operate in both the research and clinical context. We strive to isolate the differences between research and clinical process flows in the umbrella layer. As a result, the laboratory LIMS become relatively agnostic as to whether they are servicing a research or clinical process. This enables GIGPAD to provide an important translational medicine function. When geneticists identify a clinical use for a research technology, we can quickly enable well validated clinical IT support for that technology's workflow – in the case of resequencing microarrays, one person was able to affect this transition in less than a week. While workflow support can be established very quickly, creating the necessary quality assurance / quality control (QA/QC) functionality can take longer. GIGPAD contains a case management system (CMS) that is responsible for: (1) supporting the wet bench work that is required to break a sample into the required constituent assays, (2) managing the QA/QC functionality which often involves performing specific follow-on assays on a second technology to validate results and (3) managing the laboratory signoff process that occurs in advance of results being sent to geneticists. We have found it worthwhile to continuously focus a significant amount of our development resources on improving and building new forms of automation into the CMS. The processes that the CMS supports cover a significant percentage of the cost of genetic testing. They are also important in ensuring the test quality.

GIGPAD has been operational in our environment since April of 2004. As of September 10, 2008 there were 1,007 registered users of the system and 1,076,379 data files under management. GIGPAD currently provides support for the initial phase of the Molecular Diagnostic testing process. This includes all steps up until the point that we determine

what genetic variations are present in the stretches of DNA that are sequenced. At this point GIGPAD forwards this information to clinicians for interpretation (Figure 3). GIGPAD is designed to handle DNA based, RNA based or protein based testing efforts.

***Supporting the Geneticists: GeneInsight and the Genomic Variant Interpretation Engine (GVIE)***

Most clinicians have neither the training nor the time to assess the clinical significance of variants that have been identified in their patients. For this reason, molecular diagnostic laboratories typically employ genetic professionals who interpret test results and produce a text report describing the significance of any genetic variants identified. The process of generating this report can be time-consuming and expensive, so streamlining and automating portions of the process through IT can be valuable. IT can also help standardize result reporting by reducing variability between the ways different geneticists might interpret the same result. When test results are sent to the EMR, it is useful to capture interpretations in structured form in addition to the genetic variants themselves. Capturing structured interpretations requires IT support during report generation.



**Figure 3: Applications Used to Support Molecular Diagnostics within Partners**

We have constructed two tools to support the report generation process in our environment: GeneInsight and the Genomic Variant Interpretation Engine (GVIE). Because our understanding of the clinical implications of particular variants can change over time, it is important to have a database that tracks current knowledge relative to individual variants. We use GeneInsight to perform this function. Keeping this type of database current is extremely challenging. There are numerous heterogeneous research databases that contain information about genetic variants but very few clinically validated data sources. Genetic professionals must review these research sources to formulate clinical interpretations. GeneInsight has data structures that associate information with diseases, genes, tests, and genetic variations. When a new test is brought on line, developers load data from existing data sources. GeneInsight is then integrated into the geneticists' reporting processes so that it is maintained as a by-product of the process of signing out reports. This is made possible through integration with GVIE. GVIE is a reporting tool that is interfaced to GIGPAD. As variants are identified in patients, they are passed to GVIE which then looks up the information stored in GeneInsight on those particular variants. GVIE then produces a draft interpretive report which a geneticist and/or genetic counselor reviews. During this review process, they are shown statistics related to the variant's frequency and given the ability to review previous cases where the variant was identified. Geneticists and genetic counselors have the option of modifying

these reports. We track which reports are modified. This provides us with a metric for assessing the maturity of each part of GeneInsight.

As a result of this process, geneticists can maintain the data in GeneInsight for the diseases they report on without a significant incremental time investment when they encounter a new variant. As a benefit, the time required to report on previously identified variants is significantly reduced. Overall, the combined GVIE/GeneInsight system saves geneticists time, which promotes systems utilization. The amount of data contained in GeneInsight has grown over time and we are now evaluating additional uses for this information in the clinical environment. However, as we will describe later, we need to find ways to dramatically increase the depth and breadth of the data in GeneInsight if it is to solve our core genetics related knowledge management needs.

### ***Supporting Front Line Clinicians: Electronic Health Record (EHR) and Clinical Decision Support (CDS) System Integration***

Molecular diagnostic reports are ideally delivered to the clinician through an EHR. Doing so ensures that genetic test results are stored in an organized manner and are consistently accessible to authorized clinicians. It also opens up the possibility of leveraging automated CDS systems to proactively assist clinicians in the use of this information. We created a specially secured area in our EHR where we maintain patient genetic profiles and a custom screen to organize the genetics results. GVIE is interfaced, through our hospital pathology LIMS, to this part of our EHR. This interface allows us to transfer genetic laboratory test results in both human readable and highly structured electronic formats. The structured genetic test result format is designed to be read by CDS algorithms.

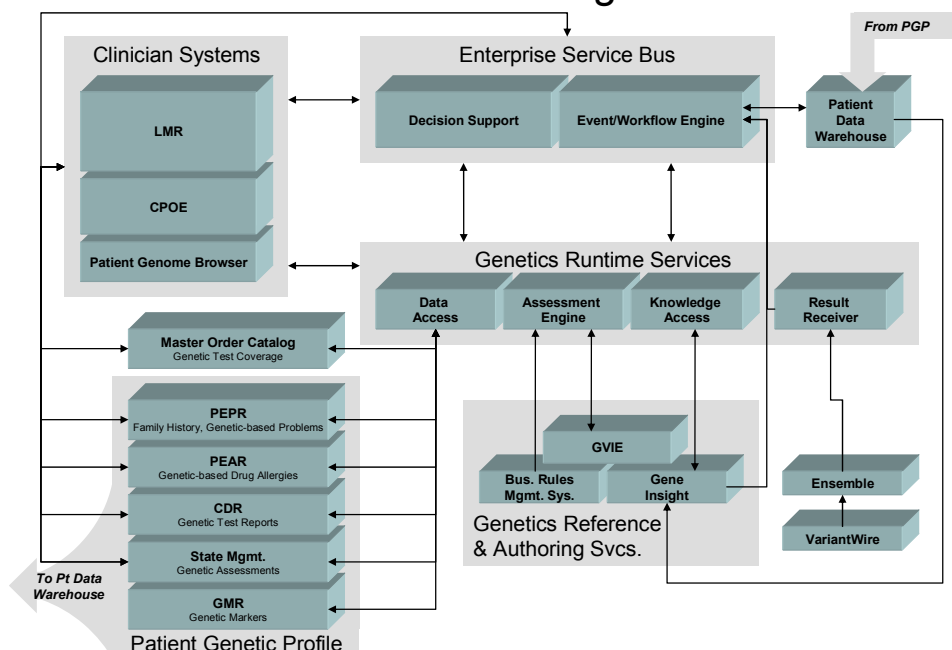
As the number of variants stored in patient genetic profiles increases, it will become increasingly difficult for clinicians to review these profiles during the care delivery process. Properly applying the information in these profiles will be even more challenging. Clinicians will need to rely on CDS functionality to surface relevant genetic information at the appropriate times. This functionality is required for gene based personalized medicine to reach its potential, but it will be very difficult to build. We have taken an initial step within Partners by establishing a genetics aware clinical decision support rule that alerts physicians if they order a particular class of tyrosine kinase inhibitors for a patient who has a genetic mutation associated with resistance to these drugs. The process of establishing this rule helped us understand the modifications to our EHR infrastructure we need to make to support broader based genetic aware clinical decision support.

The enhanced genetics IT architecture we have begun constructing is shown in Figure 4. We chose to employ a service oriented architectural (SOA). Patient genetic data will be stored in a specially secured Genetic Marker Repository (GMR). Test definitions will be stored in a Genetic Test Definition Catalog (GTDC). GeneInsight will serve as the EHR's genomics knowledgebase. A service layer will be constructed on top of these repositories. Our general CDS infrastructure will leverage these services as will our front end EHR displays. An additional display in the form of a Patient Genome Explorer

(PGE) will be constructed to provide clinicians with an additional specialized view into patient genomic profiles. We are focused on constructing the GMR, GTDC, PGE and GeneInsight wrappers in a modularized fashion. Our goal is to ultimately package the GMR, GTDC, PGE and GVIE/GeneInsight components together to form a Genetics Enabler Kit (GEK) that could be used to genetics enable other EHRs, PHRs or Pharmacy systems.

The test results stored in the GMR and the knowledge in GeneInsight are the heart of this architecture. While the information stored in these repositories is critical, the inter-institutional interfaces required to populate them do not currently exist. The next sections describe the network infrastructure we are constructing to help address this problem.

## PHS Genetics Enabled Target Architecture



**Figure 4: PHS Genetic Enabled Architecture Currently Under Construction.** LMR, Longitudinal Medical Record; CPOE, Computerized Physician Order Entry; PEPR, Patient Enterprise Problem Repository; CDR, Clinical Data Repository; GMR, Genomic Marker Repository; PGP, Patient Genetic Profile; GVIE, Genomic Variant Interpretation Engine.

### *Linking it all Together: Establishing the Data and Knowledge Flows Needed to Drive Genetics Aware CDS*

We have established a flow that links together GIGPAD, GVIE, GeneInsight and our EHR. When a Partners HealthCare patient is tested in our Laboratory for Molecular Medicine (LMM), the results flow into our EHR in structured form. Up to date knowledge about the implications of any variations found by the LMM is maintained in GeneInsight. When we test our own patients, we have both the knowledge and data resources required to construct genetics based CDS.

Genetic tests are performed by many different laboratories throughout the world. Many of the genetic tests performed on our patients are performed by external laboratories. Similarly, our diagnostics laboratory often tests patients for other providers. In both of these cases, interfaces do not exist to transfer the variants identified in electronic form. Therefore, neither the structured genetic data nor the structured knowledge is ultimately represented in an EHR. Without this information, CDS is impossible.

This problem must be addressed by both establishing appropriate standards and creating appropriate data and knowledge networks.

### ***Establishing the Standards for Genetic Data Exchange***

A member of the HPCGG IT team serves as one of the co-chairs of the HL7 Clinical Genomics Workgroup. We have developed and contributed internal message formats to HL7 and worked with them to develop a standard model to transfer genetic laboratory test results. We have also worked extensively with the leadership of LOINC to establish appropriate coding schemes for genetic results and their associated clinical implications. We also interact with government institutions focused on supporting the development of standards for personalized medicine data and health record functionality including the Department of Health and Human Services, the National Library of Medicine's Lister Hill Center for Biomedical Communication, and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative.

In addition to developing standards, we are also investing in two infrastructure projects designed to facilitate the exchange of genetic data and knowledge.

### ***VariantWire: A Network for Moving the Data***

Interfaces between laboratories and provider EHRs are expensive to build and maintain. In the case of a reference laboratory serving the majority of a provider's clinical testing needs, this cost can often be justified based on the volume of tests that pass through the interface. However, the genetic testing market is dispersed. In the majority of cases, a single interface between a provider and a laboratory will not carry enough volume to justify the cost. It would be economically infeasible to establish point to point interfaces linking every provider to every genetics laboratory that tests their patients. Standardization efforts can substantially reduce the costs of establishing interfaces, but these costs will always remain significant. Unless this issue can be addressed, it will be impossible for providers to maintain patient genetic profiles that contain all variants identified through laboratory tests.

We are constructing a system, called VariantWire, which is designed to serve as a hub that will enable the secure transfer of genetic test results. Any institution that connects to VariantWire will be able to communicate with all other connected institutions through a single interface. In this way, VariantWire can help address the "many-to-many problem." The economics of creating interfaces to VariantWire should continuously improve as additional providers and laboratories connect. Each additional node should increase volume through existing interfaces and thereby reducing the transaction costs of



maintaining those interfaces. VariantWire is constructed on top of Intersystems' Ensemble product. We are building validation functionality into the hub that will enable us to enforce standards by rejecting any non-conforming messages. We are currently in the process of linking together the HPCGG LMM, the Intermountain HealthCare EHR and will link the PHS PGE when it is completed.

We are currently designing an interface between the GEK and VariantWire. Once this interface is built, any EHR that leverages the GEK will be able receive structured genetics results from any laboratory on the VariantWire network without any additional software development. We hope the GEK will be leveraged in this way to dramatically reduce the costs associated with joining the VariantWire network and thereby increase network participation.

### ***Leveraging GeneInsight to Create a Knowledge Network***

VariantWire is designed to enable EHRs to gather complete patient genetic profiles where every variant identified in a patient is stored in a GMR. However, just knowing patient specific variants is not sufficient to fully enable EHR's to handle genetic information. Structured knowledge detailing the significance of variants is also required. A laboratory can report its assessment of the significance of a variant at the time a test is run. However, over time additional information may be learned about the significance of a variant. Mechanisms must be built into the EHR to make this knowledge accessible. Some laboratories make an effort to update their historical reports when new knowledge is discovered but this solution is not scalable for tactical and strategic reasons. From a tactical standpoint, laboratories can go out of business, laboratories usually cannot "follow" a patient when they change providers, and providers may or may not agree with the knowledge sources leveraged by the laboratory. From a strategic standpoint, as the breadth of DNA covered in each genetic test increases, it will become infeasible for individual laboratories to curate knowledge for all of the variants their tests can identify. Providers face a similar issue. In our environment GeneInsight serves as our genomic knowledgebase. Our geneticists continuously update GeneInsight as they learn more about individual variants. However, they only maintain information on genes covered by our LMM tests. No single institution could ever hope to employ enough geneticists to maintain up to date information on all of the variations that could be identified in its patient population.

It is impossible to genetics enable an EHR in a scalable manner without access to comprehensive, continuously updated, genomics knowledge. This information will clearly be needed to maintain broad spectrum genetics aware CDS but it will also be needed to perform more basic functions. For example, as the amount of data in the GMR grows, we will need to provide filtered displays of the data through our PGE. We will need to rely on the knowledge in GeneInsight to keep these filters up to date over time. We are also working to build a flag into our PGE that alerts clinicians if new information has been learned about a variant since it was reported. This flag will be driven off of the information in GeneInsight.

Genetic knowledge will continue to be curated by many different institutions for the foreseeable future. A mechanism is needed to assemble the knowledge curated by many disparate groups and make it accessible to EHRs, PHRs and pharmacy systems. We are exploring whether GeneInsight could be enhanced to enable this knowledge network. The concept we are investigating involves building a central GeneInsight hub and then distributing instances of GeneInsight that can communicate with this hub. Each participating organization would gain the ability to enter three levels of data into GeneInsight:

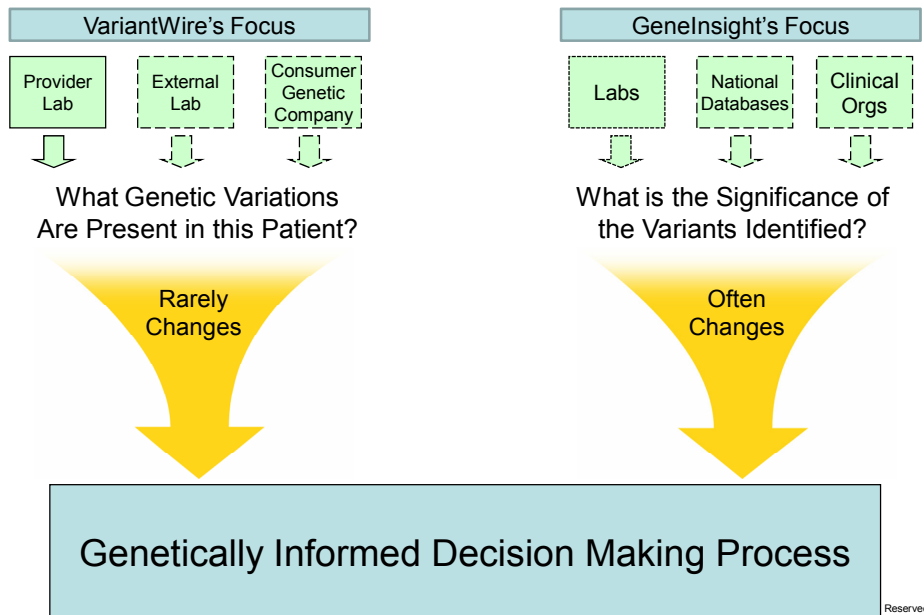
1. Public Data: information that can be shared with any organization that has access to the GeneInsight network.
2. Private Data: information that is never transmitted to the centralized hub and therefore remains proprietary to the organization that enters it.
3. Protected Data: information that an organization is willing to disclose under certain conditions. Potential conditions could include a fee per use, a subscription fee or through a collaborative agreement.

Our goal is to support the business models required to incent organizations to share protected data.

EHRs, PHRs and pharmacy systems could implement an instance of GeneInsight. Because GeneInsight is a component of the GEK, any organization implementing the GEK would have access to the GeneInsight network. Connected organizations would gain access to public data and have the ability to negotiate access to protected data if they desire. Each organization will presumably also specify the degree to which they trust the different data sources that contribute to GeneInsight.

We are seeking partnerships with commercial genetic testing laboratories, healthcare providers as well as pharmaceutical and biotechnology companies to assess the feasibility of implementing the tools that we have developed within their environments and in creating the networks described above.

# Information is Dispersed



**Figure 5: VariantWire and GeneInsight Areas of Focus**

## Summary

We have implemented and are pursuing several genomics related IT projects because we believe that in the long term they will enable significantly improved patient care. Physicians have a limited amount of time to spend with each patient. Genomic technologies are capable of generating an overwhelming amount of data and our knowledge of the implications of these data constantly expands. A robust inter-institutional IT infrastructure must be established to enable clinicians to harness the increasing power of genetics for the benefit of their patients.

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doi:10.1371/journal.pbio.0050254

# **HealthMapRx** Washington, D.C.

## **COMMUNITY-BASED APPROACH TO PERSONALIZED HEALTH CARE: HEALTHMAPRx™**

A Patient Self-Management Program Utilizing Community-Based Pharmacists  
Summary Document

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### ***Program Overview***

HealthMapRx™ is a service of the American Pharmacists Association (APhA) Foundation. The service has evolved from the previous decade of research by the Foundation, including the “Asheville Project®,” a community pharmacy-based program that began in 1996 and continues today. (1) The success of this model has helped business leaders to recognize that health care can be an investment in well-being rather than an expense for sickness.

HealthMapRx™ is a patient-focused collaboration between employers, their covered health plan beneficiaries, and specially trained community pharmacists who provide, face-to-face counseling sessions where participants learn how to better manage their chronic conditions (such as diabetes, high blood pressure, hyperlipidemia) and reduce associated health risks.

Local networks of pharmacists are established to provide the self-management services to the patients. The program is collaborative and designed to *complement and reinforce* existing health care team provider roles, including the patient’s primary care physician. In addition, the program establishes a benefit model that aligns incentives for employers, patients, and providers.

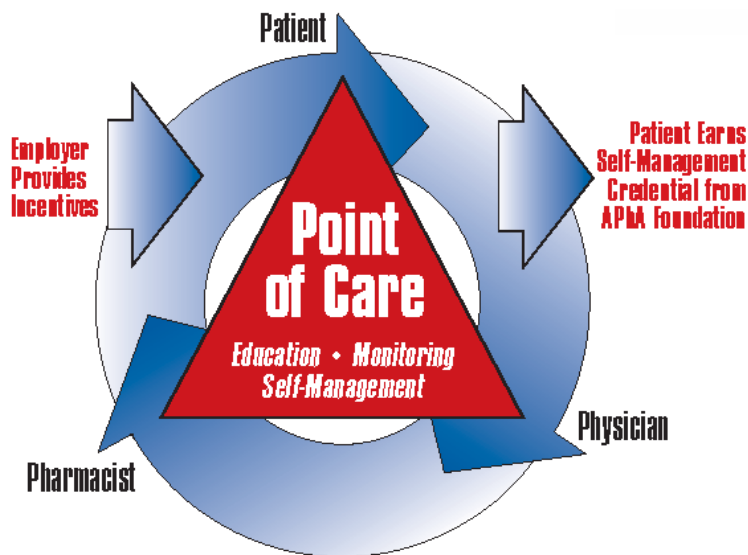
### ***What the Program Does: The Value Proposition***

- The **HealthMapRx™** program creates a collaborative team of employers, employees, pharmacists, physicians and diabetes educators — and aligns

incentives — to focus on wellness, patient self-management and workplace cost savings.

- **Educates and supports employees** with information and guidance to become active participants in managing chronic diseases, such as diabetes, based on a proven model and demonstrated research outcomes.
- **Employer waives co-pays on medications** or provides other incentives to encourage active engagement in self-care.
- **Employee (or dependent beneficiary) meets regularly with pharmacist** to discuss their care and learn new ways to monitor and control their disease.
- **Centers care around the patient** and positions pharmacists as accessible, valuable resources in helping patients understand and control chronic disease.
- **Reduces unscheduled absenteeism** in the workplace and associated costs.
- **Improves health outcomes** as measured by key indicators.
- **Saves health care dollars** by investing in patient well-being — keeping people healthy rather than paying for care when they become seriously ill.

### *How the Program Works*



- **Specially trained community pharmacists** “coach” participants on how to manage their chronic disease, including setting goals, using medications properly, and tracking their condition consistently with recognized clinical indicators such as cholesterol tests, blood pressure, foot exams and eye exams.

- **Collaborative care teams** — including pharmacists, diabetes educators and physicians — are assembled in the community, educated about the program and are compensated for their involvement. Team members communicate regularly to optimize patient care.
- **Employees choose to participate** through a voluntary benefit offered by their employer that aligns employee benefit incentives to encourage success.
- **Success is measured** with the following indicators:
  - improvement in A1C concentrations (blood sugar control)
  - body mass index
  - blood pressure control
  - lipid control
  - increased patient satisfaction with pharmacy services
  - decreased costs of medical care

### *The Model*

#### *Employers/Payers*

The practice model implemented for HealthMapRx™ is designed as a collaborative care model that emphasizes the roles of the employer, physician, pharmacist and patient. The employer/health plan agrees to invest in incentives for patients and pharmacist providers. At a minimum, these incentives include waived co-pays for medications and certain supplies. Some employers add other incentives as a way to integrate the program into their existing plan offerings. Other incentives have included counting participation toward wellness points, waiving co-pays for education classes and/or laboratory test co-pays. Most employers participating in the program are self-insured employers.

Employers work closely with their Third Party Administrators (TPA) and Prescription Benefit Managers (PBM) in order to establish a process to implement incentives (such as waived co-pays) and to provide basic claims data information on an annual basis to allow for program economic performance review. In some situations, the TPA or PBM can assist the employer with other aspects of program implementation, such as sending announcement letters to potential participants or managing enrollments.

#### *Participants/Patients*

Enrollment is voluntary; the employer educates eligible beneficiaries about the program through various announcement methods, including direct mailings, e-mail, newsletters and live orientation sessions. All participants are required to complete enrollment materials and a participant agreement. Enrolled participants are matched with a pharmacist “coach” and/or location from a local pharmacy network directory.

#### *Pharmacists*

Patient assignments are coordinated by a local pharmacy network coordinator. Services may be provided in a local pharmacy or at the participant’s workplace. During regularly

scheduled visits, pharmacists apply a prescribed process of care that focuses on clinical assessments and progress toward clinical goals, establish self-management goals specific to each patient, and work with other health care providers and may recommend adjustments in the patients' treatment plans. Pharmacists who participate in the program are required to complete an ACPE-accredited training program in the relevant clinical area (such as diabetes or hypertension), or are otherwise certified. They generally follow national treatment guidelines unless otherwise specified by the physician. Pharmacists collect subjective and objective assessment information and enter it into a web-based documentation system for outcomes reporting. Pharmacists are reimbursed by employers for patient visits according to fee schedules negotiated by the local pharmacy network.

### ***Physicians and other Providers***

Physicians are informed of participant enrollment and are encouraged to share their care plan with the pharmacists, who reinforce that plan with the participants. Pharmacists communicate with physicians after every visit, as necessary, and refer patients as needed to their physician (for follow-up visits, laboratory tests or resolution of medication-related problems), or other providers, such as a dietician (for intensive nutrition education) or diabetes education centers (for additional education support).

### ***Program Experience***

The HealthMapRx™ Program evolved from early published works in Asheville, North Carolina and the APhA Foundation's Project ImPACT Hyperlipidemia (1, 2, 3, 4). Since that time, the APhA Foundation has conducted projects in a variety of sites throughout the country to assess the replicability of the model in diverse settings. Results from the initial pilot site replications were published in 2005 (See Appendix A) (5). These results demonstrated positive clinical, economic and patient satisfaction improvements for participants enrolled in the program. In order to test the scalability of the program, the APhA Foundation launched the *Diabetes Ten City Challenge* at the end of 2005. The interim clinical results were published in March, 2008 (6). Currently, the program is implemented under the brand name, HealthMapRx™. The program has now been implemented by more than 80 employers in 20 states, with more than 3,000 active participants. Several employers are continuing the program into multiple years.

The majority of employers implementing the program have been self-insured and include private companies, school districts, city and county municipalities, and health systems. Program design has core elements that are required to ensure the integrity of the model, but there is significant opportunity to tailor the program and its implementation at the local level. The HealthMapRx™ team provides implementation consultation for employers, as well as templates for announcing the program and for managing enrollment.

### ***Success Factors***

There are key qualities that seem to drive successful program implementations:

- An Employer/Payer that will invest in incentives for patients and providers to improve health and lower costs

- Employers who are more involved in the program implementation, and have an open culture with their employees tend to have faster and higher percentage of enrollments of eligible beneficiaries
- Receptiveness of health care providers who support community-based collaborative care
- A local network of pharmacists that have the motivation, training and time to help patients manage their care
- Accessibility to pharmacist services
- Following the HealthMapRx established process for employer implementation, patient care, and documentation
- Willingness of TPA/PBM to provide claims data for analysis

### **Challenges**

The program is implemented at the local level and developed to address needs, resources, cultural and political issues within the employer’s community. Thus, challenges may occur at the local level. Although some employers have unique challenges, there are some challenges that appear to occur more frequently. For example, an employer “champion” usually drives the initial approval and implementation of the program. If there is a change in staff or lack of a true “champion,” this is challenging and may even jeopardize continuation of the program. Without strong employer support and a plan for consistent and clear communication about the program benefit design for participants, the full enrollment potential (and therefore, results) may not be realized.

On the pharmacist network side, since this is a relatively new practice model for community-based pharmacists, it is important to balance participant access with network capacity. In addition, there needs to be adequate resources to support network services, coordination, and management. The pharmacist provider shortage, particularly in rural areas can also be a challenge.

### **Employer Profile**

In order to implement the program, employers should have the following characteristics:

- Willingness to invest in employees’ health to enhance quality of life, reduce sick days and lower hospitalization costs;
- Willingness to promote the program, orient and enroll patients;
- Capability to (or use a PBM) provide reduced/waived co-pay prescription cards or other incentives;
- Ability to provide access to data from TPA to track total health care costs for enrollees; and
- Willingness to provide payment to pharmacist providers/the provider network.

### **Patient Profile**

When employees enter the program, they are asked to sign a participant agreement, which outlines consistent requirements for their patients who participate. Generally, the program is introduced as a voluntary benefit for employees and/or dependents who agree to meet with a qualified pharmacist on an ongoing basis for education, monitoring and set



personal goals for diabetes self-management. The patient agrees to work with pharmacist coaches to set goals and monitor their progress. Participants must agree to meet at least quarterly with a qualified pharmacist to set self-management goals, have scheduled assessments and procedures to monitor performance.

### ***Pharmacist Provider Profile***

Specially trained pharmacists or those willing to complete the required training are recruited to pharmacy networks as providers for the program. Providing medication therapy management services, including identifying and preventing drug-related problems is a key component of the pharmacist's role. In addition, pharmacist providers have received additional training in chronic care and the program processes of care. Examples of requirements include:

- Pharmacists must have designated certification or completed a comprehensive ACPE-accredited program in diabetes or other disease state as specified (such as a CDE, BCPS certified or APhA Diabetes program certification).
- A private consultation area must be available for patient education.
- Self-management coaching to patients in relevant lifestyle areas, such as smoking cessation, diet, exercise and nutrition must be provided.
- There must be collaboration with local health care providers, including primary care physicians and refer, or recommend for referral, participants to existing resources.
- Outcomes documentation must be maintained.

### ***Other Health Care Providers***

It is important to stress that, in this program, physicians will remain responsible for overall care of patient and changes in therapy. Physicians will receive summary reports after each patient's session with the pharmacist as applicable, and will be notified about the program when patients enroll. Physicians are still responsible as required to make therapy changes or referrals as required. Data from the early projects indicate that physician outpatient and diabetes education center visits increase.

### ***Summary***

A collaborative practice model utilizing community-based pharmacists to provide coaching and self-management education to patients, that aligns incentives for participants, sponsoring employers and health care providers has been successfully implemented in a variety of settings. An investment in "well care" has led to lower costs, improved employee satisfaction, and better outcomes for patients with chronic disease.

## **HISTORY OF HEALTHMAPRx™(Appendix A)**

**The following milestones and research have paved the way for HealthMapRx™**

- 1996** The APhA Foundation creates **Project ImPACT: Hyperlipidemia™**, the first collaborative care program designed to show how pharmacists, physicians and patients with high cholesterol can work together to make

lifestyle changes and improve medication adherence to achieve cardiovascular goals. (4) Over a three-year period, nearly 400 people with high cholesterol in 12 states, working together with 26 pharmacies, participated in this landmark program.

The results, published in the *Journal of the American Pharmacists Association* in 2000, showed that more than 90 percent of patients stayed on their medications and 67.5 percent reached the National Cholesterol Education Program (NCEP) treatment goals.

- 1997** The diabetes management program, the **Asheville Project**, is first offered to employees, dependents and retirees in the City of Asheville, North Carolina, in partnership with the North Carolina Center for Pharmaceutical Care. The program starts with 47 initial participants.
- 1998** Mission-St. Joseph's Hospitals and the Blue Ridge Paper Company add the diabetes management program for beneficiaries in their health plans. It grows to more than 300 people with diabetes over the next three years.
- 2003** Long-term results of the Asheville Project, published in the *Journal of the American Pharmacists Association*, showed that patients improved A1C levels (key diabetes indicator), employers had lower total health care costs, employees had fewer sick days and increased satisfaction with pharmacist services, and pharmacists developed thriving patient care services. (1) Asheville Project results also appeared in *Business Insurance* and *The Washington Post*.
- 2003** The APhA Foundation begins follow-up research based on the Asheville Project and **Project ImPACT: Hyperlipidemia™** to assess the feasibility of expanding the model to multiple employer types and geographic locations. A pilot program, "**Patient Self-Management Program™ for Diabetes**," is initiated in four states at five employer sites with more than 300 patients.
- 2004** The APhA Foundation completes development of "**The Patient Self-Management Program™ Diabetes Credential**," the first and only credential for education in diabetes that can be awarded to individual patients for completing study in diabetes and its management as part of the Patient Self-Management: Diabetes™ program research.
- 2005** **Patient Self Management Program™ for Diabetes** program results are published with compelling findings that indicate the ability to replicate and expand the scale of the Asheville model in diverse settings (5):
- Participants dramatically improved in key indicators of diabetes control, including reducing average A1C values from 7.9 to 7.1 percent, using the goal set by the American Diabetes Association

- More patients kept up to date with key indicators of diabetes care, including influenza vaccinations, foot and eye exams, recorded blood pressure, and lipid profiles (average increase of more than 40 percent)
- Employers realized a \$918 net cost savings per employee

**2005** **Diabetes Ten City Challenge™** is announced in October, inviting participation from employer groups that want to seize the opportunities for improved patient health and cost savings demonstrated in the Asheville Project and Patient Self-Management Program™ for Diabetes. The Pittsburgh Business Group on Health and the Northwest Georgia Healthcare Partnership are the first employer groups selected to participate.

**2006** **HealthMapRx™ is established.**

**2008** **The Interim Results of the Diabetes Ten City Challenge are published in JAPhA (6)**

The report released analyzed aggregate data on 914 DTCC participants who were in the program at least three months as of September 30, 2007. It documented clinical improvements in all the recognized standards for diabetes care, including:

- Decreases in laboratory measures (mean) for hemoglobin A1C (a laboratory test showing the patient's average blood sugar control over the previous two to three months), LDL cholesterol and blood pressure over the initial year of the program
- Increases in the number of participants with current influenza vaccinations, foot examinations and eye examinations
- 21% increase in the number of participants achieving the American Diabetes Association goal of A1c level <7.0
- Increase from 43.8% to 57.7% in participants achieving nationally recognized National Cholesterol Education Program goals for LDL cholesterol
- 15.7% increase in the number of people achieving recognized goals for systolic blood pressure
- The number of DTCC participants who felt their overall diabetes care was “very good to excellent” increased from 39% to 87%
- More than 97% of participants reported being “very satisfied” or “satisfied” with diabetes care provided by DTCC pharmacists
- The number of participants setting self-management goals to control their diabetes also increased significantly: those with nutrition goals increased from 22% to 66%; those with weight goals increased from 23% to 64%; and the number of participants setting exercise goals increased from 24% to 72%

### ***HealthMapRx™ Testimonials***

#### **Pharmacist Testimonial:**

*Society and even families don't realize how bad this disease is. They often don't know that uncontrolled diabetes can lead to blindness, amputation, end-stage kidney disease,*

*and cardiovascular complications such as stroke or heart attack. It's important that patients can access a coach on a regular basis to help them through the ups and downs and help them control their diabetes as best they can. You can't just show someone how to use a glucometer and send them on their way – it takes constant education, encouragement, and support to empower the patient to self manage. Our participation in this pharmacist directed wellness program gives us a chance to give back to the community by providing much-needed diabetes patient education and make a difference in the health outcomes of people with diabetes. Pharmacists have the ability to apply their scientific knowledge in making therapeutic decisions that will affect health outcomes.*

*In the first three months of the program we ideally like to see the patient once a month to understand their health history, set goals, and go over basics like nutrition, exercise, and how to use a glucometer. We see what patients need in terms of education and make sure they understand what each medication does and how to take it.*

**Employer Testimonial:**

*This program enables people to understand what they need to do in order to become healthy or stay healthy. The more that people take advantage of it, the healthier our employees will be, which can be a win for everybody. Improving health means improving energy and attitude, and there is less down time from lost workdays.*

*Everyone I have talked with who is involved in the program has been pleased with their results, whose personal encouragement helped recruit employees to the program. They tell me they have learned more about diabetes than ever before.*

**Patient Testimonial:**

*The program is a good support to help you stay on track, and an excellent resource for information. Having an hour set aside allows me to sit down, focus and ask questions without feeling rushed. I take three different medications, and the pharmacist explained what each one does in my body. I also learned that my medications might not have been working right because of how I was taking them. I probably wouldn't have asked my doctor about that.*

*My morning readings were very high, Working with (my pharmacist), my doctors increased the dosage of medicine I take at night, had me take it with my meals and have a snack before I go to bed. I've been able to bring down my numbers and work on losing some weight, which has been a major factor. I feel much better.*

*When I found out I had diabetes, I was devastated. Since enrolling in this program, I've made major changes in my life, including losing weight and exercising every day. My pharmacist coach has become one of my closest friends and she continues to inspire me at every visit. This program has taken away so much of my fear and truly saved my life.*

**Physician Testimonial:**

*The key to success of the program is to make sure that additional burden isn't placed on the physician for managing these patients. Physician engagement is driven by the*

patients, and they will respond best when they hear from their patients why this is a huge benefit.

## How the Program Works

**APhA Foundation** contracts with employers to implement its HealthMapRx program which include program guidelines, templates and software for documentation. The Foundation also provides staff support and assists with identifying a local network of pharmacist providers to establish the program in the selected community.

**Employers** offer a voluntary employee benefit with incentives to encourage success (typically waiving participants' co-payments for diabetes medications and supplies) and compensate pharmacists for the care provided.

**Participants** meet regularly with a specially trained pharmacist "coach," learn how to self-manage their diabetes and track key indicators with medical tests, foot exams and eye exams.

**Pharmacists** are specially trained and use the Patient Self-Management Program to educate patients and record their clinical progress on key diabetes quality-of care indicators.

**Collaborative care teams** including pharmacists, diabetes educators and physicians communicate regularly to optimize care.

**Success is measured** by evaluating:

- improvement in clinical outcome indicators, such as A1C concentrations (blood sugar control)
- increased patient satisfaction with pharmacy and diabetes care services
- decreased costs of medical care.

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# **Marshfield Clinic** Marshfield, Wisconsin

## **Community Based Approaches to Personalized Health Care: Marshfield Clinic**

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**This is an abbreviated version of the paper prepared for the Department of Health and Human Services Summit on Personalized Health Care, October 5–7, 2008. The full paper can be requested from the Director, Marshfield Clinic Research Foundation, 1000 North Oak Avenue, Marshfield, Wisconsin 54449.**

### **I. PIONEERING**

On September 19, 2002 Wisconsin Governor Scott McCallum joined the leadership of Marshfield Clinic and its Research Foundation (MCRF) in announcing the enrollment of the first of what would be 20,000 research subjects into the Clinic's Personalized Medicine Research Project (PMRP). Governor McCallum stated in his remarks:

“Marshfield Clinic and its research division are dedicated to the public good, using science, scientific research, and scientific discovery to improve the quality of life in Wisconsin, throughout the nation, and really, throughout the world. I congratulate the people of north central Wisconsin for their understanding of the importance of research to our health and well-being, for their commitment to participation in research, and for the community spirit shown in efforts to promote health and the health of future generations.”

The President of Marshfield Clinic, Frederic Wesbrook, MD, summarized for the audience the objectives of the research project, which was supported by \$2 million from the State government, \$800,000 from the Federal government, and \$1 million from Marshfield Clinic.

“This project seeks to accelerate the reality of personalized medicine, a concept that envisions an individually tailored approach to detecting, preventing, and treating disease based on a person's specific genetic profile. Some day your doctor will have a set of genetic tests that will tell you personally what diseases you are at risk of getting, what you should do to prevent or delay those diseases, and what medicines you should take or not take.”

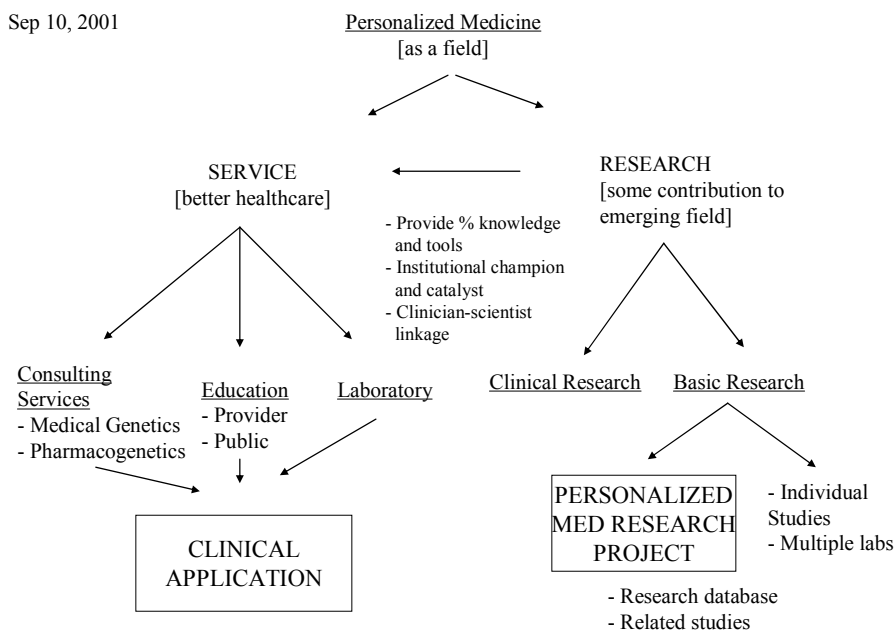
The start of PMRP enrollment was preceded by almost 2 years of planning. The Clinic's potential to contribute to personalized medicine was first realized and the vision created



by Michael Caldwell, MD, PhD, then the Director of MCRF and PMRP's first principal investigator (PI). The grant proposals were prepared and the project organized by MCRF's Associate Director, Steve Wesbrook, PhD. PMRP was executed beginning with enrollment by Catherine McCarty, PhD, MPH, then Director of the newly created Personalized Medicine Research Center and currently the project's PI. The project's inception, design, and implementation were guided by a steering committee of co-investigators that included, in addition to those mentioned above, the Clinic's then Director of Clinical Research, Kurt Reed, MD; Director of Laboratory Medicine, Robert Carlson, MD; Director of Medical Genetics, David Schowalter, MD, PhD; Director of Corporate Communications, Donna Chapman-Stone (responsible for community and population information and education); and Clinic's Chief Information Officer, Carl Christensen. The team received advice and counsel from an Ethics and Security Advisory Board (ESAB), which was led by Norman Fost, MD from the University of Wisconsin, and a Scientific Advisory Board (SAB), which was lead by David Altshuler, MD, PhD from Massachusetts's Institute of Technology and Jurg Ott, PhD from the Rockefeller University.

Between a meeting of the ESAB in August 2001 and the first meeting of the SAB scheduled for September 13 and 14, the PMRP team was wrestling with a fundamental question raised by the ESAB. "Is the Marshfield Clinic Personalized Medicine Program [as it was then titled] a service program or a research program?" At the recommendation of the ESAB, the name would be changed and the focus narrowed, in large part out of the need to be clear to research study participants that they would not be receiving any personalized medicine services. Below is an unedited slide (Figure 1) that was sketched by the Associate Director of MCRF to guide the discussion of this question at a meeting of the steering group on Monday, September 10, 2001.

**Figure 1. Outline of Personalized Medicine**



This working slide still remains a reasonable outline of the dimensions of personalized medicine. But what was perhaps most prescient about it was the recognition that even though the boundaries of PMRP would be narrowed to research, 1) the research project would serve as a catalyst for implementation of personalized medicine throughout the Clinic and 2) would create new linkages between scientific investigators and clinicians. What no one could predict, of course, was how much the United States would be changed by the events of the next day.

For the October 5-7, 2008 personalized health care (PHC) Summit in Utah, Marshfield Clinic was asked to focus on “how a community-based healthcare system has brought the key elements of PHC together to deliver more effective health care.” In doing so, we will address three elements of PHC: biomedical informatics; clinical care, including medical genetics and laboratory medicine; and medical research. The final section will provide some insights from our limited perspective that may have general import on future change and also address four of the major initiatives that are defining the PHC way ahead at Marshfield Clinic.

## **II. BIOMEDICAL INFORMATICS**

In 1964 a group of physicians at Marshfield Clinic determined that the future of high quality health care would depend on computers. The Clinic has held to that vision for the past four decades and, as a result, developed one of the largest regional integrated health care information systems in the nation. The system spans most of the northern half of Wisconsin and is used by over 12,000 users, not only Marshfield Clinic employees, but also affiliated hospitals and treatment centers, and even competing physician group practices. The information network maintained by Marshfield Clinic has been structured in parallel to the health care delivery process and is of strategic importance in an effort to provide consistent, quality health care to a large geographical area. Marshfield’s ability to develop information systems has provided the needed flexibility to react to evolving clinical needs in a rapid manner and has assisted in point-of-care decision support for PHC.

**Where We Are Today.** Effectively delivering PHC requires many different systems working in concert at Marshfield Clinic. These include:

- Regional, integrated electronic health record (EHR)
- Semantic interoperability
- Clinical data warehouse
- Decision support
- An Internet-based portal that enables patients to directly interact with the Clinic’s information systems
- Tablet computers
- Population-based tools

**Leveraging Clinical Information Systems to Support PHC Research.** Marshfield Clinic believes that PHC is a process of continually improving knowledge and care, not a single endpoint. To that end, Marshfield has a history of integrating clinical computing with research computing.

- Population-based research. Marshfield Epidemiological Study Area (MESA) is a geographic population cohort in a 24 ZIP code area. The MESA database tracks a

- subject's geographical location since 1991 and has the ability to link subjects to data stored within the Clinic's data warehouse.
- Development of the Personalized Medicine Research Database (PMRD). PMRD leveraged existing Marshfield Clinic practice management and laboratory systems to recruit and collect genetic specimens. A cryptographic key system was developed to allow genotypic and clinical data to be combined for research studies, while protecting the privacy of research subjects. PMRD was created to store specimen sample identification numbers and the corresponding subject identification information. Later, PMRD was modified to accept validated genotype and phenotype data from the data warehouse.
  - Phenotyping efforts. One essential requirement in assessing genetic impact on health and disease is the ability to characterize reliable phenotypes. Strong informatics and data management techniques, clinical guidance, statistical expertise, and clear communication with the disease experts enhance the ability to generate thoughtful and accurate phenotypes.
  - Data mining. MCRF has entered into several collaborative data mining ventures with scientists from the University of Wisconsin-Madison to analyze large complicated genetic and phenotypic databases and develop algorithms that can predict patient reactions and outcomes to treatment.
  - Episode-of-care. System monitors events in the EHR for patients who require special handling.

**Challenges and Future Directions in Biomedical Informatics.** The most important lesson we have learned is that systems to support PHC are not something that can be purchased “out-of-the-box” or simply “bolted-on” to existing systems and processes. They require commitment that spans years or decades. Achieving PHC requires a commitment to change, not only computer systems, but also health care processes. This implies that practicing clinicians must be involved at all stages of the development and implementation lifecycle. Another lesson is that the necessary integration cannot be achieved by silos, each focusing only on its own needs. Managers of clinical systems must believe that research is of value to the entire organization. Similarly, researchers must take the time to understand the ever-increasing demands on health care providers. It is acutely obvious to everyone at Marshfield Clinic that converting health care records to electronic form and eliminating paper charts (something that took 40 years to achieve) is only the first step toward a health care computational infrastructure that truly enables the vision of PHC. Marshfield Clinic is actively engaged in many projects to keep working toward the vision.

- Anonymized research data warehouse. The objective of this project is to develop a data warehouse that contains genetic, environmental, and clinical data.
- Natural Language Processing (NLP) of clinical documents. With over 55 million electronic documents containing health habits, family history, symptoms, environmental, and social factors, Marshfield Clinic is actively advanced in NLP to extract additional information for phenotyping and decision support.
- Phenotyping advances. Tools and techniques to improve the efficiency and interoperability of the phenotyping process are being developed.
- Pedigree mapping. Pedigrees add power to the genetic studies and allow rare disease studies to be conducted with limited cases.

- PHC reference library. The reference library will provide information on clinical, environmental, and genomic data and validated phenotypes.
- Research web portal. An Internet-based application (portal) that enables researchers to access genotype, clinical, and environmental information will be developed.
- Optimizing care through integration. Systematic workflow analysis and process mapping techniques are needed to seamlessly integrate not only the EHR, but also research innovations and discoveries into a busy practice setting.

### III. CLINICAL CARE

#### Clinical Medical Genetics

Medical Genetic Services at Marshfield Clinic. The Medical Genetic Services Department at Marshfield Clinic provides clinical genetic consultation, diagnostic testing, and genetic counseling for patients and their families with genetic concerns. The greatest demand for clinical genetic services in adults is for single gene disorders including inherited cancers (*BRCA1*, *BRCA2*, *HNPCC*, *FAP*); connective tissue disorders such as Marfan syndrome, hemochromatosis, cardiomyopathy, Brugada, hemoglobinopathies, Huntington's disease; and genetic susceptibility to adverse drug reactions. Annual unique patient referrals to Medical Genetic Services have grown from <30 in 1999 to over 300 in 2007.

The clinical genetics team realizes how important it is to raise awareness among patients regarding seeking genetic services, and has received grant support to increase the patient's understanding about the value of genomic medicine. The initiative, led by Christina Zaleski, MS earned her the 2007 Leadership in Excellence Award for Community Service. The project involved creating multilingual (English, Spanish, Hmong) brochures and posters that discuss when and how to access genetic counseling for families with high-risk newborns or those who have experienced miscarriages, a stillbirth or other infant death. These materials were distributed to all birth centers in Wisconsin.

Utilization of genomic medicine to provide optimal clinic care requires that practitioners feel comfortable with ordering and interpreting genetic test results, as well as discussing these results with patients and their families. To help increase the awareness about medical genetics among primary care providers in Wisconsin and encourage practitioners to utilize clinical genetic services, Marshfield Clinic offers an annual state-wide conference entitled "Practical Genetics for Health Care Providers."

The future of clinical medical genetics. With PHC emerging as an important contribution to clinical care, it is important to sustain and grow clinical genetics as a state-of-the-art service to both patients and healthcare professionals. The American Board of Medical Genetics is in the process of expanding the role of clinical geneticists and suggesting that geneticists broaden their services to liaison with other departments and be viewed as a resource for primary care patient management. It is also critical to attract students to consider careers in genetic counseling.

While genetic medicine has largely centered on provision of diagnoses and treatment for individuals with well-defined single gene disorders, genomic medicine when fully

realized will decipher genetic information derived from a person's genome into predictors of disease susceptibility. A personalized medicine approach can be implemented for a particular individual and may consist, for example, of avoidance of certain disease risk factors or implementation of various screening modalities. Pharmacogenomic advances will facilitate testing for multiple genetically-mediated drug sensitivities, and genetic counseling will be needed for patients and their family members to understand the relationship between drug metabolism capacity and genetics that underlie them. Prospective genetic testing will be invaluable to the primary care provider in planning appropriate treatment.

To realize the promise of genomic medicine, health insurance barriers need to be overcome. Genetic referral and testing represents an exclusion in many insurance policies. Insurance denials entail additional workloads to genetics professionals, and in some instances appeals need to be made by the patient and not the healthcare provider. In order for patient care to be optimized there needs to be a three-way transfer of information between clinicians, researchers, and community members. PMRP has influenced interconnectedness between clinical care and research through its Community Advisory Group (CAG) and quarterly Personalized Medicine News (Figure 2). Accurate family histories from patients is challenging for many reasons. Bioinformatics approaches appear to have great promise.

**Figure 2. Personalized Medicine News**

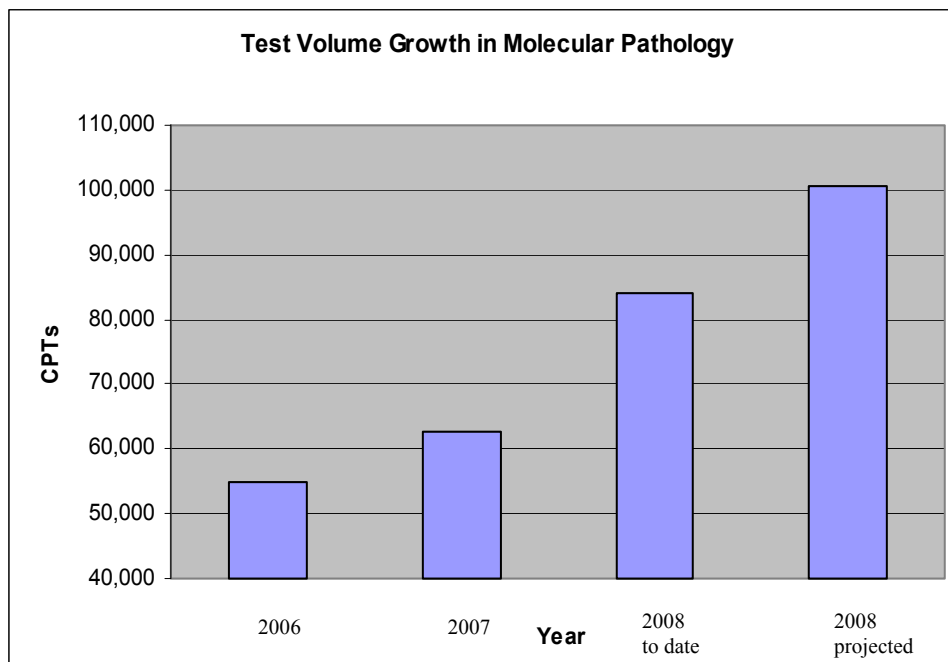


## Laboratory Medicine

Where we are today. Advances in genomics and related technology in the past decade have resulted in significant growth in molecular diagnostic testing and services, which has impacted almost all areas of laboratory medicine. Marshfield Laboratories was an early adopter of molecular diagnostics and has been performing such testing for over 12 years. As molecular testing increased in breadth and crossed into more traditional lab sections, it became apparent that for a regional laboratory, such as ours, to rapidly adopt this technology, a core laboratory with expertise in molecular testing was necessary. In 2005, Marshfield Laboratories formed its molecular pathology section to expand, coordinate, and standardize this growing area of testing services utilized for bacteriology, virology, coagulation, hematology, genetics, histology, and pathology. Prioritization of resources for development, validation, and implementation of new molecular testing is determined with input from clinicians and laboratory personnel representing all these areas. Test volumes in molecular pathology have grown faster than any other areas of the clinical lab during this time period (Figure 3).

The Molecular Pathology Laboratory is continuing to develop improved automation and expanding test menus. PHC tests in the area of oncology are increasingly prevalent, as these treatments are very expensive and carry high risks. Identification of KRAS gene mutations in codons 12 and 13 can predict whether or not an epidermal growth factor receptor (EGFR) inhibitor will be useful to treat colorectal cancer. A challenge for our laboratory to offer this testing is that the only commercially available testing product in the U.S. is labeled RUO (“for research use only”). Regardless of how well the test is validated, the use of RUO reagents in clinical testing significantly reduces or eliminates most forms of third party reimbursement. In the overall scheme of patient health care, it is clear that identifying patients who will not respond to costly treatments is prudent. However, KRAS mutation test reagents alone cost approximately \$100/test. With little hope of reimbursement, the laboratory’s financial prospects of this testing are bleak. Our implementation of JAK2 testing to identify myeloid proliferative disorders, such as polycythemia vera, has been similarly hampered because the company holding exclusive intellectual property rights for clinical testing offers only RUO reagents for sale. These are not isolated instances.

**Figure 3. Test Volume Growth in Molecular Pathology**



Challenges and future directions in laboratory medicine. Biomarker discovery has proven to be much more difficult than initially envisioned. In addition, many new markers are part of a complex interaction with other genes and environmental influences making clinical utility difficult to ascertain. Also, while great strides have been made in the technology involved in DNA sequencing and genotyping, the availability of accurate phenotypes is lagging far behind. Another significant hindrance to bringing new molecular testing into the clinical laboratory is affordability, which is often linked to gene patents. Also, the complexity of patent and intellectual property regulations limits availability. The costs associated with advanced medical technology for PHC are disproportionately higher than traditional diagnostic services. If PHC is to grow,

healthcare institutions, Centers for Medicare and Medicaid Services, and insurance providers must recognize the overall healthcare savings of PHC and support testing through appropriate reimbursement.

#### **IV. GENETIC RESEARCH**

**Personalized Medicine Research Project.** PMRP was designed to support genomics research in three areas: pharmacogenetics, genetic basis of disease, and population genetics. The project required a concerted effort to develop not only genotyping and phenotyping capability and informatics infrastructure, but also needed to address issues such as logistics of population-based enrollment, bioethics, and stewardship of the biobank. From its inception, the project was intended to serve as a national resource for hypothesis generation and testing.

Nearly 20,000 adults have enrolled as of August 2008. Over 99% have consented to be re-contacted. In addition to the extensive EHR, the temporal span in years of clinical data available for PMRP subjects sets the cohort apart from other similar projects. The average span of clinical history for PMRP participants is 29+ years.

**Pharmacogenetics.** The study of the genetic impact on drug metabolism and disposition, and how this translates into drug efficacy or contributes to adverse drug events, has been a research priority at Marshfield Clinic. Below are ongoing extramurally-funded pharmacogenetics research studies.

- Efficacy and safety of statins
- Genetic impact on metformin metabolism and management of patients with type II diabetes
- Pharmacogenetics of tamoxifen response in treatment of breast cancer
- Pharmacogenetics underlying response to beta blockers in patients with glaucoma
- Pharmacogenetics of warfarin metabolism

**Genetic Basis of Disease.** Outlined below are ongoing extramurally-funded studies being conducted at Marshfield Clinic on the genetic basis of disease.

- Cataracts
- Scoliosis and other vertebral malformation
- Genetic and environmental interaction and risk factors contributing to multiple sclerosis
- Myocardial infarction risk and influence of genetic variation on chromosome 9p21

In addition, Marshfield Clinic investigators are conducting internally funded studies using the PMRP research infrastructure in hypertensive heart disease, Alzheimer's disease, fibromyalgia syndrome, and osteoporosis.

#### **V. THE WAY AHEAD**

Marshfield Clinic is a robust, comprehensive and highly integrated health care system. It has over 750 physicians and 6,500 additional staff at 41 centers in a primary service area that includes 60% of Wisconsin geographically. Annually, the Clinic sees approximately 370,000 unique patients. In support of its mission to serve patients through accessible, high quality health care, research, and education, Marshfield Clinic supports strong

programs in research and graduate education, maintains its own 147,000 member HMO, and provides through its Community Health Center and other programs health care for people irrespective of their ability to pay. But the capability of even a large and progressive health care system to deliver PHC depends largely on external factors, including the general advancement of science, speed with which industry commercializes discoveries, intellectual property law, government and private medical insurance payment schedules, and many others.

To the degree to which Marshfield Clinic can control its own PHC future, it will continue to do what it has done well over the past decade. This includes striving for even better integration of medical research and clinical practice. Marshfield Clinic and MCRF are either leading or substantially contributing to a number of new initiatives that will also shape its way ahead.

### **Clinical and Translational Science Awards (CTSA)**

University of Wisconsin School of Medicine and Public Health and MCRF partnered to receive a NIH Clinical and Translational Science Award in September 2007. Currently supporting a national consortium of 34 academic medical research institutions, plus partnering institutions, CTSA is scheduled to link 60 such institutions by the year 2012. The consortium has been designed to ensure broad access to CTSA resources, enhance communication, and encourage information sharing.

Marshfield Clinic also joined in the fall of 2007 with five academic health science schools/colleges at the UW-Madison to create the UW Institute for Clinical and Translational Research (ICTR). ICTR was established to “create an environment that transforms research into a continuum from investigation through discovery and to translation into real-life community practice, thereby linking even the most basic research to practical improvements in human health.”

### **Wisconsin eHealth Care Quality and Patient Safety Initiative**

On November 2, 2005, Wisconsin Governor Jim Doyle came to Marshfield Clinic to sign Executive Order 129 creating the Wisconsin eHealth Care Quality and Patient Safety Board. Governor Doyle charged the Board with establishing an action plan for the statewide adoption of EHRs and the exchange of health care information by the year 2011 (<http://ehealthboard.dhfs.wisconsin.gov/>). Referring to the Clinic’s leading role in developing and using EHRs, its successful quality initiatives, and its history of championing for health care reform, he stated that “Marshfield Clinic is truly the place to make this announcement.”

Whereas progressive and committed organizations can do much on their own, no single institution has enough information on all their patients to provide optimal health care, and health information exchange cannot be done by a single institution. A statewide eHealth information infrastructure will improve the quality and cost of health care in Wisconsin by 1) ensuring health information is available at the point of care for all patients, 2) reducing medical errors and avoiding duplicative medical procedures, 3) improving coordination of care between hospitals, physicians, and other health professionals, 4) furthering health care research, and 5) providing consumers with their health information to encourage greater participation in their health care decisions. The goal is to achieve

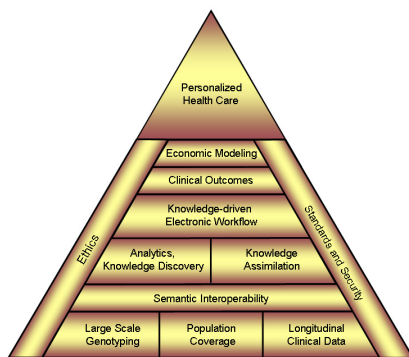


100% electronic health data exchange between payers, health care providers, consumers of health care, researchers, and government agencies as appropriate.

### Personalized Health Care Testbed

Achieving the computational infrastructure for PHC will require the integration of many different components. It will also require two very different types of research endeavors. The first type of endeavor will involve research groups that have deep expertise in one, or a few, of the components. These groups will develop new theories and approaches to specific problems in PHC. For example, one of these groups may develop improved knowledge discovery tools and a health care workflow engine. Essentially, these groups focus on one piece of the puzzle. The second type of endeavor will involve the development of a PHC Testbed (Figure 4). The number of potential PHC interventions is likely to increase exponentially in the coming years. The role of a PHC Testbed is to evaluate the impact of implementation of possible PHC interventions in real clinical practice, at a speed that is more rapid and at a cost that is much below what would be required by a *de novo* conventional clinical trial. Testbed institutions will need to have expertise across a broad range of domains.

**Figure 4. Personalized Health Care Testbed Architecture**



There are three foundation components in a PHC Testbed: large scale genotyping, population coverage, and longitudinal clinical data. Potential PHC interventions that will be evaluated by a PHC Testbed can be divided into major groups. The first are those that involve associations between genetic or metabolic markers that are measured by existing broad screening tools, such as large-scale SNP chips. The second base-level attribute of a PHC Testbed is population coverage. Having a large and stable population base allows prior information to be applied to future clinical care in a large percentage of cases. The third base level competency for a Testbed site is an extensive repository of longitudinal clinical data. Since the future of PHC is certain to include lifetime EHRs, attempting to evaluate PHC interventions without many years of prior clinical data can yield spurious results.

The next level in the PHC Testbed is semantic interoperability. Without a consistent framework for what individual clinical terms and concepts mean, it will be impossible to reliably identify patients or evaluate outcomes. Above the semantic layer is the knowledge layer, which includes two components, analytics and knowledge discovery and knowledge assimilation. The process of defining clinical phenotypes and clinical outcomes involves the use of knowledge discovery techniques. Any successful PHC

Testbed must have an active knowledge discovery group that can rapidly address new questions. Knowledge assimilation is the process of incorporating structured knowledge from outside an organization into the computational knowledge framework of the institution. Any PHC Testbed will need a structured approach to knowledge assimilation so that new PHC intervention can be incorporated efficiently into the institution's knowledge base.

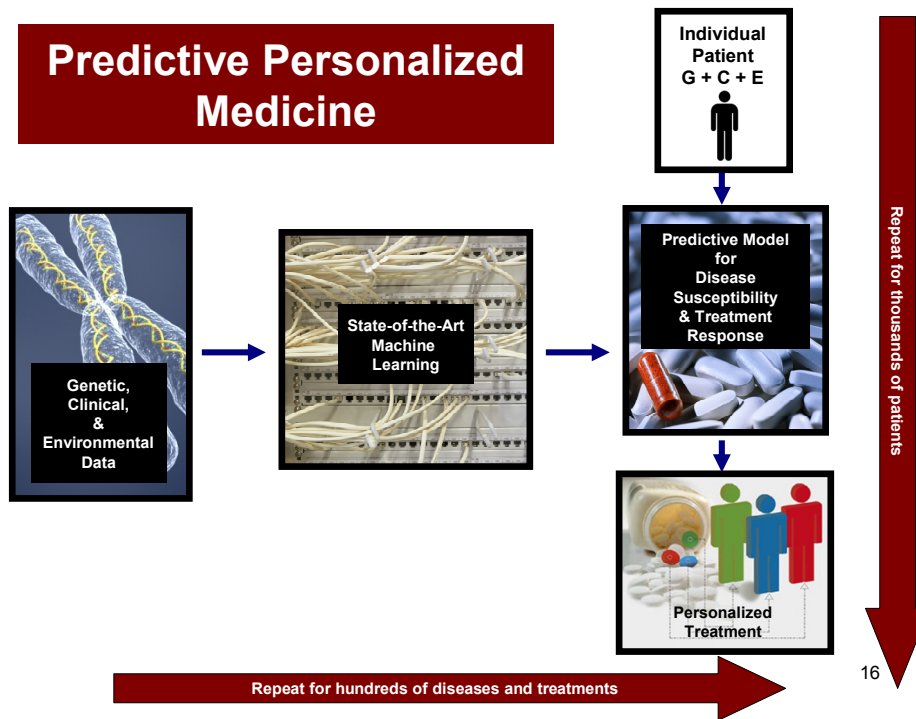
Clinical care involves complex processes with multiple steps. Simple rule-based systems are inadequate to capture these clinical workflows. The implementation of PHC will require the implementation of electronic workflows that support the complex, multi-actor nature of clinical care. The ultimate goal of PHC-driven electronic workflows is to improve clinical outcomes. PHC Testbeds will need both experience evaluating clinical outcomes and access to comprehensive data in order to determine true outcomes. This is much easier in sites with stable patient populations and broad population coverage. Two other components of the PHC Testbed span all levels: ethics and security and standards.

For PHC interventions to become mainstream therapy, they will need to be evaluated not only in highly controlled studies but also in a real world practice setting, like those represented by a PHC Testbed. A successful PHC Testbed will require expertise in such a broad range of domains. Many institutions have strengths in one, or a few areas, but very few have strength across the entire spectrum required for a PHC Testbed. However, the success of PHC will be markedly delayed if such PHC Testbeds are not available. Marshfield Clinic represents a unique combination of capabilities across this spectrum.

### **Wisconsin Genomics Initiative (WGI)**

On October 10, 2008 Wisconsin Governor Jim Doyle announced the Wisconsin Genomics Initiative, which is a collaborative research effort among Marshfield Clinic, Medical College of Wisconsin, University of Wisconsin School of Medicine and Public Health, and University of Wisconsin–Milwaukee. He stated that “By capitalizing on the unique strengths of each institution, we have a rare opportunity to meet an important scientific and public health need that could otherwise not be met.” The vision of WGI is to be able to predict for individual patients in a clinical setting the risks of disease susceptibility and treatment response using the combined power of cutting edge genetic, phenotypic, and environmental analyses, thereby making the promise of personalized medicine a reality (Figure 5).

Figure 5. Predictive Personalized Medicine



The key elements of its phase I WGI strategy are to 1) genotype up to 20,000 PMRP participants for 1,000,000 genetic markers, 2) validate selected target phenotypes and multiple clinical attributes from the Marshfield Clinic EHR for the PMRP cohort, 3) integrate genetic, phenotypic, and environmental information databases and develop the search engines to use data efficiently for scientific discovery, and 4) to build predictive computational models using machine learning and super-computer capability, for the key equation,  $\text{Genetic} + (\text{Environment and Clinical}) = \text{Phenotype}$ . It will then conduct initial predictive studies (diabetes, obesity, coronary artery disease, and atrial fibrillation) to test and improve the scientific platform, as well as a genome-wide association study (GWAS). WGI institutions anticipate making the WGI scientific platform, information, and methods available to scientists across the country. In phase II, WGI plans to add a 20,000-person urban cohort, a pediatric cohort, and to expand substantially predictive studies.

# **Moffitt Cancer Center**

## **Tampa, Florida**

### **Community-Based Personalized Health Care**

*William S. Dalton, PhD, MD; David Fenstermacher, PhD; Paul Jacobsen, PhD;  
L. David de la Parte, JD; Timothy Yeatman, MD*

#### **Personalized Cancer Care Defined**

Cancer represents the second leading cause of death as of 2005. The sequencing of the human genome has unraveled many mysteries as to how a normal cell can go awry and become cancerous. Further understanding of not only the genetics of cancer but the biology and metabolism of cancer has increased our knowledge of biologic systems that support cancer growth, and this new knowledge has been translated into novel strategies for preventing and treating cancer. And yet, these new discoveries which have heightened expectations of success, have in large part, fallen short in delivering dramatic cures anticipated by society. The reality is that we have learned that cancer is actually an array of many diseases masquerading under the single title or name of "cancer." We need to embrace the complexity of this disease we call cancer, and stop focusing on treating the cancer, and instead, focus more on caring for the patient. National policy must promote the search for solutions, not just cures. These solutions will reduce, and ultimately eliminate death and suffering due to cancer. Solutions for reducing and eliminating suffering due to cancer will be accomplished by individualizing and personalizing cancer care with the following goals:

- 1) Identification of the needs of the individual patient
- 2) Identification of markers that will predict needs and risks so that interventions can be applied earlier
- 3) Development of methods for early detection of cancer
- 4) Identification of signatures predicting which patients will not respond to standard of care therapies
- 5) Utilization of clinical characteristics and molecular profiling, matching the right treatment for the right patient
- 6) Improvement in the performance of clinical trials by patient matching
- 7) Raising the standard of care for all patients by integrating new technologies in an evidenced based approach to maximize benefits and reduce costs



At the Moffitt Cancer Center in Florida we are developing a personalized approach to cancer care we call Total Cancer Care (TCC). TCC represents a holistic approach to cancer that places the patient at the center of their life journey, as illustrated in the diagram at left.

Accomplishing these goals will require the following:

- 1) Identification of high risk populations
  - a. genetic markers
  - b. environmental factors of influence
  - c. molecular epidemiology
  - d. mathematical modeling to predict risk
- 2) Improved technology for early detection of cancer
  - a. identification of biomarkers
  - b. development of new imaging techniques
  - c. study of metabolomics
- 3) Improved therapies by utilizing multi-modality approaches designed for individuals based on molecular profiling of tumors and analysis of treatment tolerance
- 4) New therapies for patients who do not benefit from standard therapy
- 5) Improved performance of clinical trials by reducing time and number of patients on trial by trial matching
- 6) Better methods/models of drug discovery
- 7) Reduced suffering by improving psychosocial and palliative care for patients and their families
- 8) Development of factors that predict patients at risk and providing early intervention
- 9) Creation of evidenced-based guidelines that define when to use certain technologies, and improve access for all patients

Development of large regional cancer biorepositories in parallel with the development of a related information system containing the patient's clinical outcomes data holds the greatest promise for achieving the goal of personalized cancer care. Such an endeavor will facilitate discovery of biomarkers for the identification of high risk populations, early detection, prognosis, predictors of response to therapy, new drug targets, predictors

of toxicity and late effects, and clinical trial matching. Such an effort requires prospective patient consent to participate in a trial that requests the following of patients:

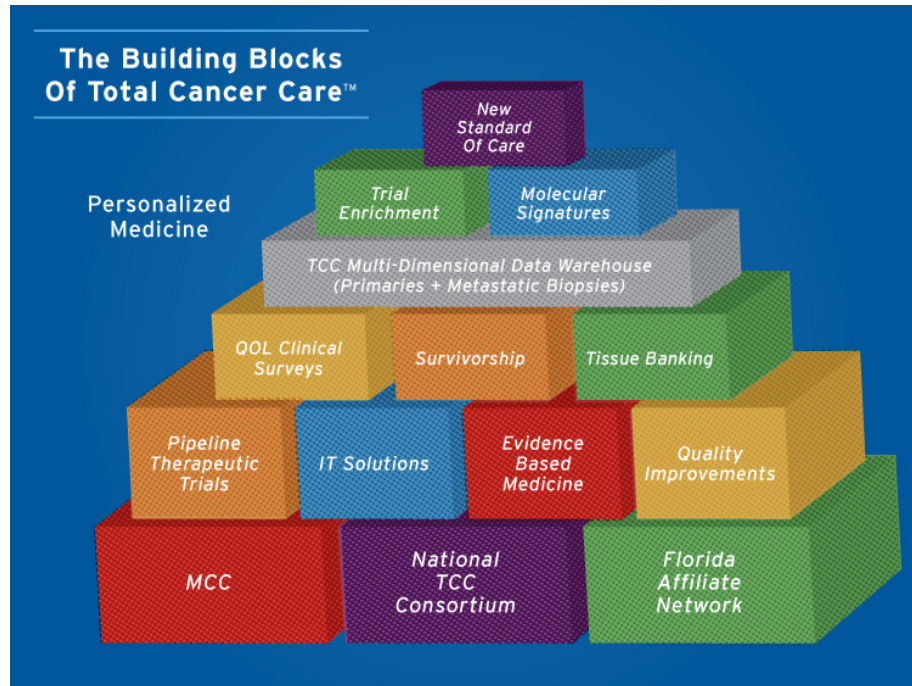
- 1) Permission to follow the patient clinically throughout their lifetime
- 2) Permission to store tumor specimens for molecular analysis
- 3) Permission to collect patient clinical data to integrate with scientific data using secure data management systems

Once created, computational approaches can be developed to compare and analyze data from all patients so that relationships can be discovered and evidence generated to develop best practices. From the evidence generated, knowledge can be derived so that effective technologies will be utilized in appropriate circumstances for individual patients to promote best solutions for their cancer disease.

### **The Road to Development of Total Cancer Care at Moffitt**

At the heart of Moffitt's Total Cancer Care™ Program is an obligation to serve as a resource to Florida communities, and the nation, in both cancer prevention and treatment. TCC seeks to overcome barriers to personalized cancer care and provide far-reaching access to the latest discoveries in lifesaving research.

The vision of TCC required three significant building blocks, among others: 1) establishing a network of partners to provide access to an NCI Comprehensive Cancer Center's expertise; 2) improving patient participation in clinical trials by matching the right patient to a trial; and 3) developing a database as a source for the collection, storage, integration and management of clinical data and scientific findings.



Our initial quest began in 1999 with the creation of a network of affiliate hospitals and physicians across the State of Florida. This network was designed to provide access to expert cancer care for patients located hundreds of miles from a comprehensive cancer center at locations closest to the patient’s home. Goals of the affiliate network partnership are to improve access to technological advances, improve quality of care, and increase participation in clinical trials. Following passage of the NIH Revitalization Act of 1993, the NIH established guidelines for inclusion of women and minorities in clinical research. This led to cancer centers making concerted efforts to expand access to clinical trials throughout their diverse communities. Establishment of the affiliate network provides the infrastructure to expand the participation of patients in clinical trials within their own communities. Building this partnership with community centers is a critical building block to our development of personalized cancer care.

Because TCC is a partnership with the patient and involves tissue acquisition and collection of clinical data, a formal protocol and patient consent process was developed. In addition, opinions of patients, patient advocates as well as bioethicists were sought. The TCC protocol was developed as a comprehensive, prospective research study to acquire tumor tissue and data from cancer patients across time and was approved by the Institutional Review Board (IRB) in 2006. The information technology platform to support this massive effort was developed to provide for a highly robust “warehouse” of clinical and molecular profiling data for patients participating in the TCC project. Upon consent to participate, patient clinical data is stored over time, including results of laboratory test results, radiographic images, treatment response data and tumor molecular profiling signatures.

The information system has to integrate electronic data from a multitude of data sources, in multiple formats and ultimately be available for research and clinical uses in a highly secure environment.

The TCC data warehouse is designed to provide a disease management system that integrates clinical data into all aspects of cancer diagnosis, treatment, and care. The integration of these data, over time, will allow the ability to identify populations of patients that may be eligible for current and future clinical trials. Consequently, patients throughout the state of Florida and beyond benefit from the knowledge gained from previous patients through maintenance of an ongoing data repository, resulting in an improved quality of cancer diagnosis, care and prevention.

Taking TCC from “vision to reality” was estimated to cost over \$100M in the first five years. It became abundantly clear that innovative approaches to funding these efforts were needed. Several funding sources were considered and pursued: philanthropy, government sponsorship and private sector partnerships. Discussions began with a pharma partner who shared the same vision of developing personalized drugs for the “right patient at the right time.” These discussions led to a successful collaboration with Merck & Co. in 2006.

Capitalizing on the State of Florida’s focus on economic development and the growth of biotech in the state, Moffitt created a wholly-owned subsidiary, Moffitt Genetics Corporation (M2Gen), to focus on administering the collaboration with our pharma partner and meeting the contractual obligations of our newly developed personalized medicine venture. The investment by the State of Florida and local (county & city) governments provided additional capital and land for the construction of a state-of-the art biorepository able to house tumor, blood and urine specimens critical to the project and provide for additional expansion of the sites participating in the project. In return for the state’s investment, new jobs are being created in Tampa Bay and Florida.

### **Current State**

Since protocol approval in 2006, the TCC Personalized Medicine research project has enrolled over 20,000 patients across 16 sites; eight (8) in Florida including the Moffitt Cancer Center, and sites in seven (7) other states: Louisiana, Connecticut, North & South Carolina, Kentucky, Nebraska and Indiana. These sites were identified based on their volume of cancer patients, and shared interest and commitment to the development of personalized medicine, the willingness to offer clinical trials to patients and their infrastructure to support clinical trials operations and bio-specimen collection. Three of the consortium sites were identified because of the efforts of the NCI National Community Cancer Centers Program (NCCCP) which provided the infrastructure for biological specimen collection and clinical trial performance.

The central data warehouse is in place, receiving interfaced data from a number of systems at Moffitt including the tumor bank, cancer registry, and the clinical information system.



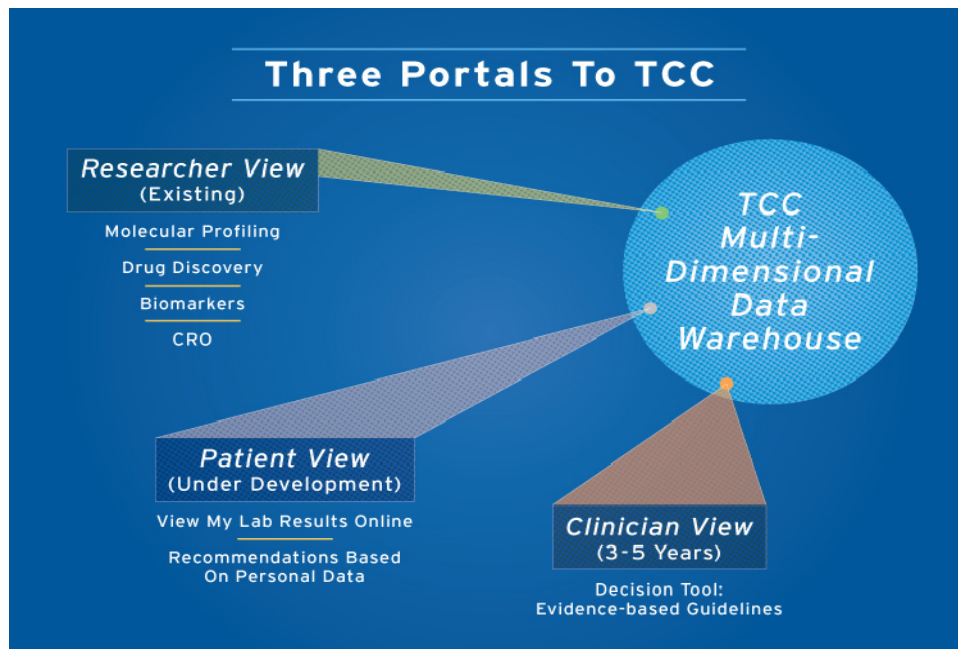
Portals to access the database are now being constructed for researchers and patients, and in the future clinicians, using the database as a decision tool.

The ability to capture data in a discreet format is extremely valuable, yet a challenging effort. As part of the project, a standardized template has been created to capture response to therapy data. This data will be critical for future research efforts in developing evidence-based, personalized treatment protocols.

Digital imaging technology and the implementation of the Emageon™ product as the DICOM-compliant imaging database for all imaging files at Moffitt provides the ability to link diagnostic images into the data warehouse. This provides the platform to implement a means to quantify response to therapy with a consistently applied methodology such as RECIST (Response Evaluation Criteria in Solid Tumors) or other modes to measure progression of disease.

Compliant and appropriate access to the data is under development that provides a single point of access and presentation to a variety of data elements. Viewing permissions and corresponding review policies and processes are essential to ensure HIPAA and human subject research compliance, while not undermining the pursuit of statistically valid research hypotheses.

An underlying premise to the information technology aspect of the Total Cancer Care™ project is meeting the data needs of various stakeholders. Although there are many others, Moffitt has initially defined three key data stakeholders in this effort, both at Moffitt and the participating consortium sites: researchers, clinicians and patients. In an effort to meet the needs of these stakeholders three portals to the data warehouse are under development. As illustrated below, these portals will allow views into the data to meet the needs of each constituent group.



The Patient Portal, currently under development, will initially focus on providing cancer survivors access to a summary of their treatment and a personalized survivorship care plan. It will also have transactional features, such as appointment scheduling and bill paying. In addition, the portal will use demographic, disease, and treatment data in the data warehouse to generate educational information tailored to the individual patient. This goal will be accomplished using a sophisticated search engine that retrieves only highly specific and relevant sets of information. The tailored educational information is expected to help patients/survivors better understand and address their ongoing psychosocial and physical needs as they move from active treatment into follow up.

The Research Portal has been constructed and is being used by basic scientists, clinical scientists, and cancer control scientists. We anticipate that the database will support research for new drug discovery targets, molecular signatures to predict therapy response and resistance, risk for relapse and new primary cancers, as well as, clinical studies for outcomes analysis.

The Clinician Portal will be developed over the next several years as a means to provide clinicians with evidence-based treatment guidelines, generated through the outcomes research conducted through TCC as well as consensus-based guidelines through NCCN or other generally accepted national standards.

An “honest-broker” system has been developed for access to data, as well as, for access to the bio-specimen repository by creating an institutional Tissue & Data Release Committee. This multidisciplinary group is comprised of faculty, Tissue Core leadership, Technology Transfer and regulatory/legal experts. A coordinator for the committee provides investigators consulting and facilitation in ensuring the research projects are appropriately defined and approved through the scientific and IRB reviews.

The bio-specimen repository supporting the TCC™ effort provides a critical resource for the development of personalized cancer care. Through the molecular profiling of thousands of tumor samples, along with blood, urine samples and corresponding clinical history, over time we will be able to identify genetic targets that can identify various cancers, develop diagnostic and prognostic tools, perform Phase-2 clinical trial enrichment and ultimately, develop a personalized approach to each patient’s cancer treatment. As of August 2008, the TCC™ project has over 8,000 tumor specimens, of which approximately 1,900 have been profiled.

Partnerships with state and local government have provided the funding for building a state-of-the-art, custom designed, fully automated freezer system with robotic capability for storage and retrieval. By 2011, it is estimated that the bio-repository will house over 3 million sample tubes: tumor tissue, normal tissue and pre/post operative liquids.

### **Challenges in the Development of Personalized Cancer Care**

Taking the development of personalized cancer care from concept to patient care is not without significant challenges, some of which are addressed briefly below.

## **Funding**

TCC requires the development of an integrated data management platform that interfaces with a broad range of information sources: electronic and paper, both at Moffitt and at the consortium sites participating in the project. As such, this effort has required a significant commitment of capital towards technology and personnel. These commitments currently exceed \$100M for the initial five years of the project. Significant additional capital, however, will be needed to sustain and advance the project.

Potential funding sources were considered and pursued, including: state, federal, philanthropy, and strategic partnerships. Ultimately, a non-traditional approach permitted us to initiate the development of TCC by creating a “win-win” scenario for the partners involved.

The state, county and city benefit through expansion of a knowledge-based economy, creation of new jobs and impact on the economy of nearly \$211M in direct and indirect income and more than \$56M in direct and induced capital investment.

Private industry benefits by access to a unique resource of human tumor samples and associated de-identified clinical data, leading to molecular and genetic signatures, novel drug targets and clinical trial enrichment.

Ultimately, the patient benefits from these financial investments through the development of personalized treatments tailored to their tumor’s genetic profile, thus increasing safety and efficacy of treatments, while decreasing toxicities.

## **Regulatory Compliance**

A complex and sometimes conflicting framework of federal and state regulations governing human subject research, patient privacy (HIPAA) and ownership of tissue and rights to intellectual property requirements govern the collection, storage, dissemination and use of human biological specimens and the corresponding patient data. Ethical considerations both medical and legal must also be applied to the use of patient tissue and clinical data for research.

This patchwork of regulation and agency guidance is a matter of concern as research is conducted using the tissue and corresponding data that has the capability of generating intellectual property and commercialization opportunities for the investigators and institutions involved. Also challenging is the management of any contractual obligations established through partners invested in the endeavor.

Recognizing the challenges faced by cancer centers in developing this research resource, in June 2007 the National Cancer Institute published the **National Cancer Institute Best Practices for Biospecimen Resources.**

The development of a clear, but broad protocol for the collection of tissue and data, along with a correspondingly clear and understandable informed consent and authorization for

use of protected health information in research is a critical first step in addressing this challenge.

All patients at Moffitt are approached with an invitation to participate in TCC, regardless of whether their care involves the collection of tumor. Patients are asked to be a partner in Total Cancer Care for life.

This vast resource and investment by the patients themselves carries with it significant moral, ethical and legal obligations to protect the participants from harm (i.e. breaches of patient privacy) and provide a benefit to these individuals who have placed their trust in us. The return for these valuable stakeholders is: a contribution to the development of advances in personalized cancer treatment that may ultimately lead to clinical trials and new drugs that will treat their specific cancer; development of evidence-based guidelines to improve the standard of cancer care and an integrated information system that will allow them access to their health information.

With the goal of ensuring the protection of the patients/research participants in TCC, and ensuring the highest quality biospecimens and their use in scientifically sound research, Moffitt adopted an “honest broker” system for their data and tissue repository.

A multidisciplinary steering committee comprised of faculty, Tissue Core staff, regulatory and legal staff functions as a means to ensure that requests for access to tissue or data in TCC are properly vetted to ensure coordination of IRB, Privacy Board and scientific reviews. Links to patient identifiers are retained only through the honest broker. Identifiable data, linked with specimens is only provided upon approval from the IRB for a specific use protocol from the tissue bank/data warehouse.

Standard Operating Procedures for the optimal collection, processing and storage have been developed to ensure the highest quality of the specimens. This is of critical importance due to the participation of sites across the country, all with varying degrees of expertise in best practices. Protocols are also necessary to standardize the procedures for the shipment of these specimens to Moffitt for molecular profiling and storage.

### **Patient Concerns**

Patients are a critical partner in the success of Total Cancer Care. We have an obligation to provide the educational tools to help patients overcome their concerns about participating in a life-long research study. Patient advocacy organizations play a vital role in helping cancer patients understand the implications of their participation and the value to them in contributing to the future of cancer research.

Equipping patients with the knowledge they need to participate in their health care decisions, including an understanding of their contribution to the development of personalized medicine requires a concerted effort.

First, patients must overcome concerns regarding the creation of molecular data (e.g. gene expression, sequencing, etc) from their tumors. Patients may fear this research identifies them as having predictive markers for developing cancer, such as BRCA1 gene mutations. It is imperative that patients, and their families, be considered major partners in the development of these resources. Ultimately, these challenges are only overcome with extensive education, communication, proper informed consent and the involvement of patient advocacy groups as well as patients themselves.

### **Changes in Physician Practice**

Health care providers across the country understand the need for highly efficient processes and practices in order to reduce costs. The development of evidence-based personalized cancer treatments requires the gathering of significant amounts of discreet data on a patient's staging, treatments and response to therapy.

This requires the creation of new data collection tools (i.e. CRFs) for the research that gathers the needed data while not interfering with the clinical care process of health practitioners.

### **Information Technology**

Although the collection of this data electronically is ideal, there is no uniformity of an electronic medical record across health care organizations and information technology capabilities vary from site to site.

The capital investment required to develop an integrated, electronic health record is astronomical and well out of reach of many community cancer centers.

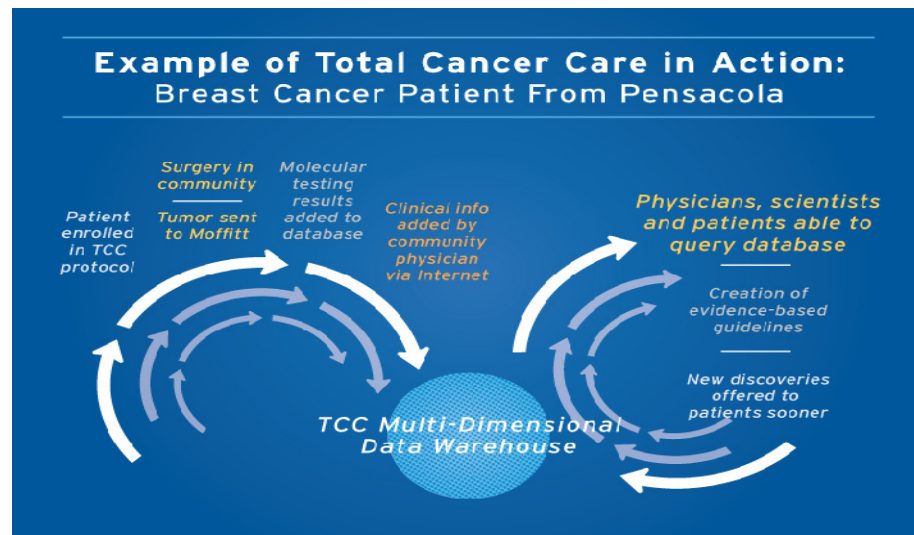
The development of personalized cancer care requires an information platform that can sustain a substantial amount of data, not only from one site but from several, while providing secure and appropriate access to the stakeholders to conduct the research leading to the discoveries that will translate to patient care. This is not only a challenge to address in terms of financial sustainability, but is a challenge to ensure the most visionary architecture is adopted to provide for data quality, security and integrity. NCI initiatives such as caBIG (Cancer Biomedical Informatics Grid) will hopefully address needs and supply solutions for these major challenges. Given the complexity of the challenge, it is also likely that solutions will emerge from private/public partnerships that address the needs of multiple stakeholders with the ultimate beneficiary being the patient and families.

### **The Future of Total Cancer Care**

In the future, we hope that the TCC™ database will be robust enough so that it can be used as a decision tool for clinicians caring for cancer patients. The figure below illustrates this concept by considering a patient diagnosed with breast cancer in, for example, Pensacola, Florida.

A newly diagnosed cancer patient would be enrolled in the TCC™ protocol at their community medical center and surgery is performed. The tumor specimen is sent to

Moffitt for profiling and entry of results into the database. As the patient undergoes treatment within the community, the database is electronically (via web) updated with the patient's discreet clinical information over time, including diagnostic images, and response data. As the number of patients in the database grows, the ability to match patients to effective clinical trials increases. In addition, as outcomes data increases, so does the ability to create evidence-based, in lieu of consensus-based, guidelines for each tumor type. Ultimately, the database would provide the stakeholders the ability to query: physicians for the most effective treatment guidelines for patients they are seeing with a particular tumor profile; scientists to develop new biomarkers and health outcomes research; and patients to have access to their own information more effectively and help them better understand their disease and treatments.



It is imperative that as many patients as possible with diverse backgrounds be entered into the database so that the variables of genetics and environment can be considered. The best approach to ensuring that the database represents the community being served is to, in fact, make this protocol and approach available to as many community medical centers as possible, and not limit participation to tertiary research centers.

### **Impact of Personalized Medicine to the Cancer Patient**

The Moffitt Total Cancer Care™ project is an ambitious approach to cancer care and research by identifying patient needs and developing solutions by integrating new technologies into the standard of care, improving performance of clinical trials, and generating evidenced-based cancer care that will increase response rates, reduce toxicity for patients, and increase access to state of the art cancer treatments within the patient's own community.

Once realized, patients participating in TCC will provide a tumor sample for profiling, their physician will be able to query the database to match the patient to optimal evidence-based guidelines, personalized for that patient. Patients will be able to query the data warehouse through a patient portal and receive their survivorship care plans and

personally relevant information regarding their cancer through a highly sophisticated search engine.

Achievement of this vision will take years and a continued investment by all the stakeholders in the effort.

<sup>1</sup> National Vital Statistics Reports, Volume 56, Number 10, April 24, 2008.  
([http://www.cdc.gov/nchs/data/nvsr/nvsr56\\_10.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf))



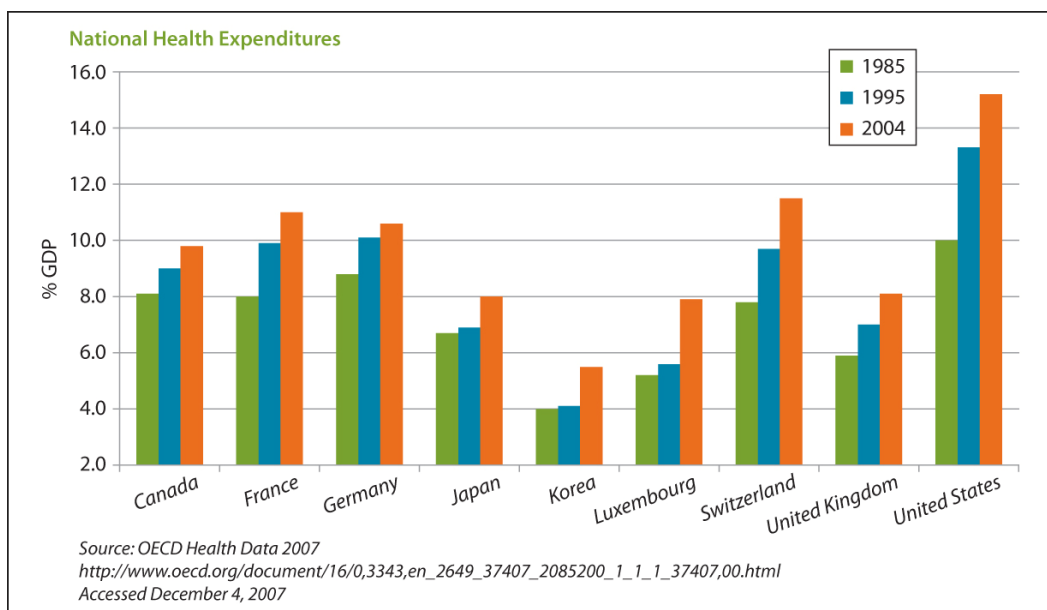
H. LEE MOFFITT CANCER CENTER & RESEARCH INSTITUTE,  
AN NCI COMPREHENSIVE CANCER CENTER - TAMPA, FL.

# Partnership for Personalized Medicine

## Arizona and Washington

*Biodesign Institute at Arizona State University, Tempe, AZ*  
*Translational Genomics Research Institute, Phoenix, AZ*  
*Fred Hutchinson Cancer Research Center, Seattle, WA*

Science and technology are beginning to provide revolutionary insights into medicine through a comprehensive molecular understanding of human health and disease. However, the promise of better health for all is undermined by the growing cost of medical treatments, which threatens the very viability of health care systems around the world. By 2015, health care spending in the U.S. is expected to reach \$4 trillion, or 20% of GDP, and by 2020, spending will double in OECD countries. The challenge we face is to use our new knowledge to improve patient outcomes while stabilizing or reducing the costs of health care. We believe that this is possible by realigning our science to meet the needs of health care.



Current economic incentives assure that companies will develop the most expensive new therapeutics and devices while neglecting the power of new diagnostics to improve health at reduced cost. The promise of personalized medicine to improve health care outcomes and reduce health care costs will not be manifest by the marketplace where incentives align with expensive therapeutics for late-stage disease. It is paramount that health care providers and

Drug	Disease	Annual cost (\$US)
Avastin	Colon cancer	\$52,000
Avastin	Lung, breast cancer	\$100,000
Gleevec	Leukemia	\$31,000
Herceptin	Breast cancer	\$36,000
Rituxan	Lymphoma	\$50,000–\$156,000
Erbixun	Variety of cancers	\$120,000

Source: USA Today, July 11, 2006



insurers play a new role in medical research, becoming the vehicle for the discovery, validation and implementation of new diagnostic platforms that can achieve the goals desired by patients and providers—prevention, early detection and effective intervention at reasonable cost.

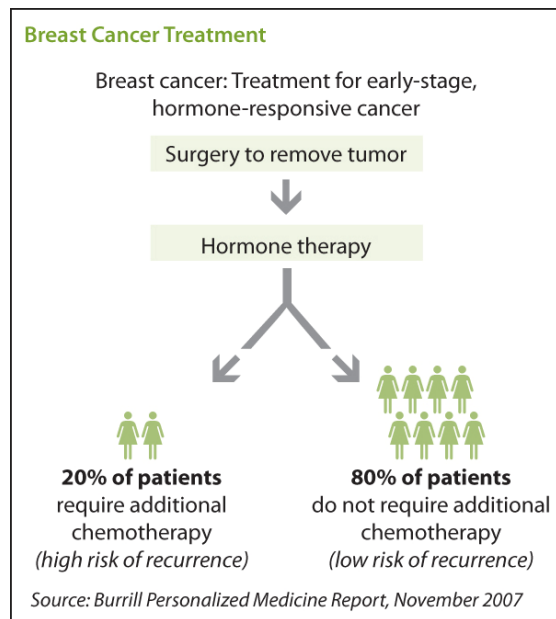
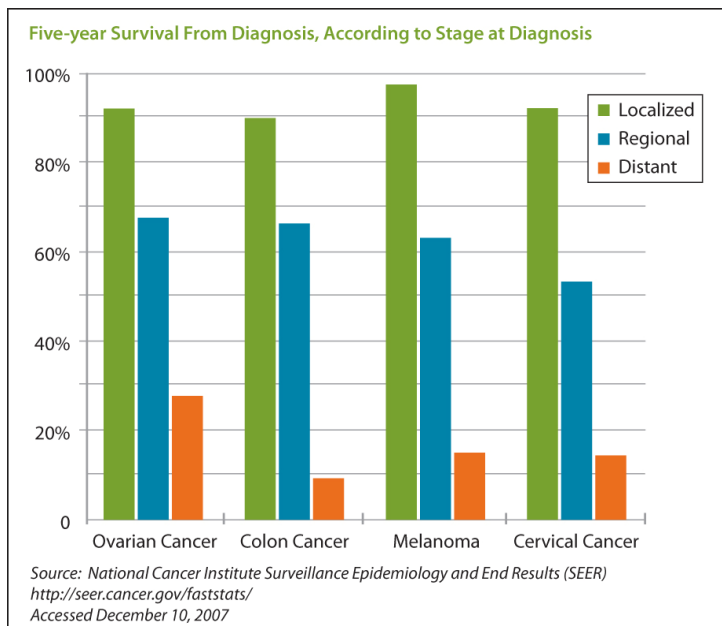
Critical opportunities exist in all diseases for better molecular diagnostics to improve patient outcomes while reducing health care costs:

- Risk assessment: Identifying individuals at greater risk of developing specific diseases will enable the implementation of preventive measures that could eliminate both the suffering from disease and the costs associated with treatment.
- Early detection: For many diseases, diagnosis at earlier stages of disease progression allows intervention when there is a greater likelihood of effective treatment and cure. For example, in nearly all forms of cancer, early diagnosis can lead to a cure at a fraction of the cost of ineffective treatments for late-stage disease.
- Definitive diagnosis: The diagnosis of many diseases is challenging due to a lack of distinctive symptoms. Improved diagnostics will allow more rapid and effective implementation of appropriate treatments for those who will benefit while preventing adverse side effects and the costs of treatment for those who will not.

**Cervical Cancer Costs**

Stage at diagnosis	Direct cancer-related costs per patient 1990-1996 (1996 \$US)
Localized.....	\$19,665
Regional.....	\$34,796
Distant.....	\$92,547

Source: Helms et al., Medical Care, 1999



Archimedes said, “Give me a lever long enough and a fulcrum on which to place it and I shall move the world.” The lever that will help health systems move health care in a revolutionary new direction is the Partnership for Personalized Medicine (PPM). PPM is a nonprofit initiative with substantial foundation support whose goal is the development,

validation and clinical application of new molecular diagnostics, designed to improve health outcomes and, importantly, reduce health care costs.

The Partnership for Personalized Medicine is led by Dr. Lee Hartwell, President and Director of the Fred Hutchinson Cancer Research Center and 2001 Nobel laureate; Dr. Jeffrey Trent, President and Scientific Director of the Translational Genomics Research Institute (TGen); and Dr. George Poste, Director of the Biodesign Institute at Arizona State University.

### How Does the Partnership for Personalized Medicine Work?

The PPM model is based on the formation of collaborative partnerships that leverage a full suite of genomic and proteomic capabilities provided by PPM with dedicated health care systems to complete demonstration projects that integrate four key elements:

- A cohesive and interactive partnership between health insurers, providers, clinicians, and researchers;
- Epidemiologic, clinical and economic analysis to identify critical intervention points in disease management;
- Systematic and empirically based discovery, development and validation of new diagnostic tests to improve patient outcomes and reduce system costs; and
- Collaborative, prospective and evidence-based evaluation of the test within health systems to validate and implement the new test in patient management.

### An Evidence-Based Approach

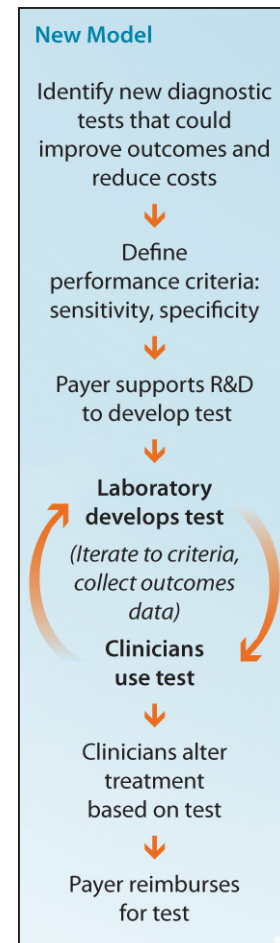
PPM features the following approaches:

#### Health care economics:

Economic analysis will identify major disease costs and opportunities for interventions to reduce costs; examples include earlier disease detection to enable preventive measures, and testing to avoid unnecessary therapy for patients who will not respond. In the current health care paradigm, the cost-effectiveness of a diagnostic test is generally not evaluated until after implementation, if at all. Thus PPM introduces a new approach whereby economic models drive diagnostic development.

#### Clinical management:

Following consultation with clinical experts, PPM will construct decision trees to outline current treatment management. A decision tree will enable PPM to identify steps in disease management that would benefit from improved diagnostics. The value of a new diagnostic will lie in its ability to better facilitate clinical decisions and prompt and appropriate intervention to improve patient outcomes. Based on models utilizing clinical, epidemiologic and economic data, the performance criteria needed to both improve



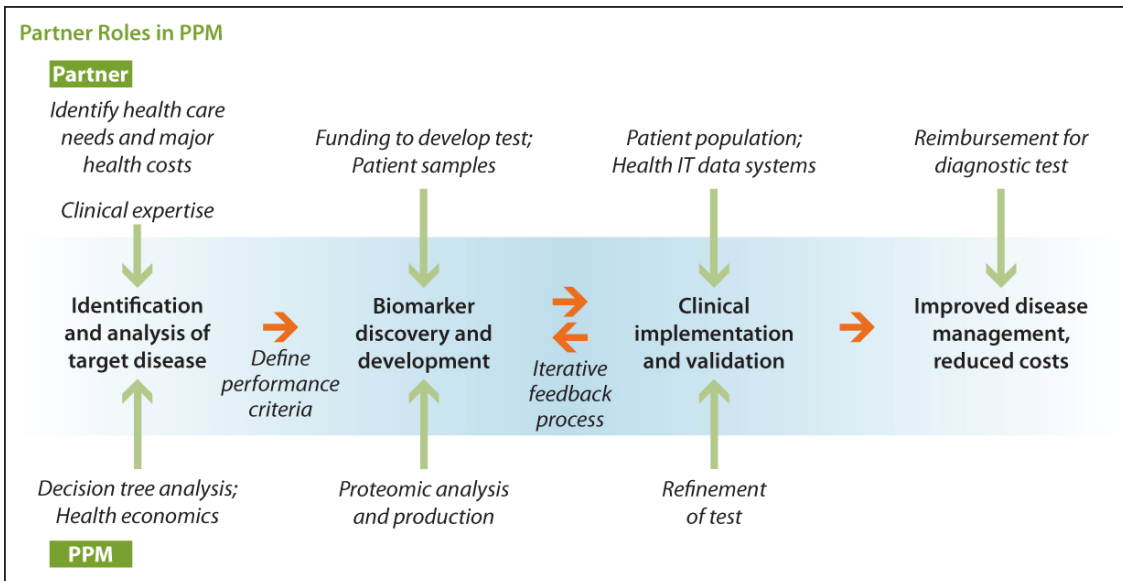
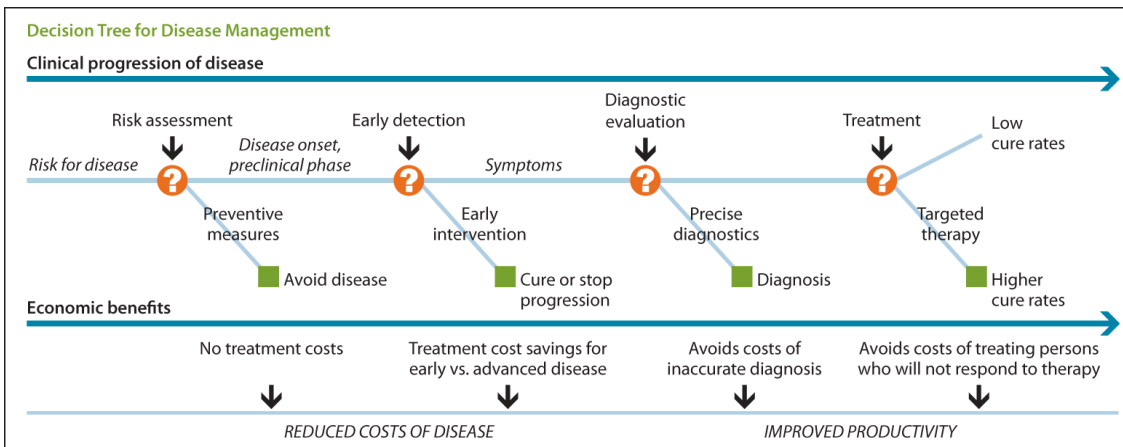
outcomes and reduce costs will be decided by all partners, including insurers, providers, clinicians, and scientists.

**Biomarker discovery:**

Research clinicians in the health care system will identify appropriate patients, obtain tissue or blood samples and record clinical outcomes. PPM will use these samples to identify hundreds of biomarkers that distinguish diseased individuals from healthy individuals. An iterative process between clinicians, patients and PPM will locate biomarkers that are sensitive and specific for the desired point of disease intervention. Markers that meet agreed upon performance criteria will move forward in the development pathway into clinical testing.

**Implementation:**

After pre-specified performance criteria have been demonstrated by prospective analysis of patient and economic outcomes, the new test will be introduced into clinical care. The insurer will then reimburse for the test. Patient outcomes will continue to be tracked, providing opportunities to further enhance test performance.



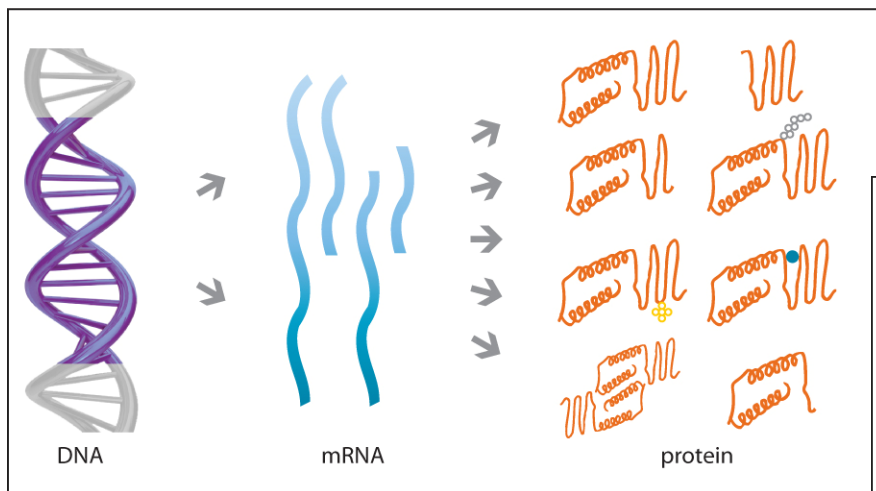
## WHY NOW? THE SCIENCE OF MOLECULAR DIAGNOSTICS

With the completion of the human genome came great expectations for personalized medicine. It was thought that discovery of genetic variations that confer significant risk for major diseases would permit the widespread adoption of preventive measures and focused screening for early disease detection. The promise has not materialized. In fact, except for rare mutations, most common genetic variations associated with prevalent diseases confer very small risk for disease. Transcriptomics, the analysis of the activity of genes in different tissues, has shown improved diagnostic capability but is complex, and clinical correlations have been difficult to reproduce. Both genomics and transcriptomics will continue to inform medical science and occasionally provide useful clinical information, but their ultimate role in personalized medicine remains uncertain.

### The Promise of Proteins

Recent advances in proteomics and improvements in mass spectrometry now make it possible to identify and quantify proteins at previously undetectable levels. This opens new opportunities for the development and application of protein biomarkers across a broad range of disease areas. It is these advances that lead us to believe that dramatic new opportunities in molecular diagnostics are at hand. Proteins are more informative than DNA or RNA as diagnostics DNA mRNA protein and can be applied to a broader spectrum of diseases for a number of reasons:

- DNA reveals only hereditary predisposition, whereas proteins change dynamically in response to physiological conditions and can reveal disease onset and progression as well as lifestyle and environmental risk exposures.
- A single gene can produce a family of 10 to 100 variant proteins. This variation adds to the amount of information available from the spectrum of proteins.
- Proteins from diseased tissue are found in the bloodstream, whereas DNA and RNA are generally obtained by biopsy of the disease tissue itself. Therefore, clinicians can measure protein biomarkers by a simple blood test that is much less invasive than tissue biopsy.



### FDG-PET

<sup>18</sup>Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) imaging of a patient with metastatic breast cancer.



D. Mankoff, Seattle Cancer Care Alliance

Protein biomarkers will also be useful in the further development of medical imaging tools such as X-rays, magnetic resonance imaging (MRI), ultrasound, and positron emission topography (PET). Combining protein biomarkers with imaging technology will enable the precise identification of disease activity within the body. However, imaging tests are expensive. Therefore, using less costly blood-based protein diagnostics as an initial step to identify which patients require imaging tests will also contribute to the reduction of health care costs.

### **Technology and Proteomics Production Facility**

To effectively facilitate the development of diagnostic tests, PPM draws upon the strengths of two of Arizona's leading bioscience entities, the Biodesign Institute at Arizona State University and the Translational Genomics Research Institute (TGen). PPM will integrate the shared expertise of these entities in proteomics, biomarker discovery, cell biology, and bioinformatics, with each bringing specific capabilities and facility resources to the collaboration. An industrial-scale, high-throughput proteomics facility will be uniquely positioned to serve as a hub for biomarker discovery. PPM will employ state-of-the-art technology platforms and research in supercomputing, nanotechnology and health economics, as well as genomics, transcriptomics and tissue sampling.

### **Technology Sharing**

The initial discovery and development work for demonstration projects will take place at the Biodesign Institute, TGen, Fred Hutchinson Cancer Research Center in Seattle and other collaborating institutions. However, technological innovations and knowledge may also be transferred to partners. Should a partner wish to establish a facility in their own country, PPM would provide support for such a venture through training and advice. This arrangement will allow partners to leverage the initial project into new disease areas, with the potential for further improvements in health care and cost savings.

### **THE BENEFITS OF PARTNERSHIP**

Partnering with PPM will offer a number of valuable benefits and opportunities:

- PPM partners will be participants in applying health care economics in their solutions, combined with the application of information technologies to track patient outcomes that are correlated with molecular diagnoses, will be integrated into the cycle of creativity.
- PPM partners will be collaborators in the effective use of genomics and proteomics to identify those at risk for disease, detect the presence of early-stage disease, match the needs of individual patients to effective therapy, and monitor for disease recurrence.
- PPM partners will join an expanding network of health care systems and laboratories dedicated to transforming the practice of medicine through the application of molecular knowledge to patient care. Partnership will provide a unique opportunity for learning, innovation and solution sharing.
- PPM partners will be able to establish their own diagnostic technology centers, enabling them to stay at the forefront of the health care revolution. PPM is dedicated to helping its partners establish their own technology capability by providing advice, best practices and training.

- As knowledge and improved methodologies become available to medicine, there will be an increasing need for governments, insurers and health care providers to develop robust policy for implementing change. Through the auspices of the Pacific Health Summit ([www.pacifichealthsummit.org](http://www.pacifichealthsummit.org)), PPM partners will have a forum for ongoing policy development.





# **University of Utah / Intermountain Healthcare** Salt Lake City, Utah

## **Pioneering a Shared Genetic Legacy**

For more than six decades, Utah researchers, institutions and citizens have collaborated to extend the boundaries of genetic understanding and its application in clinical practice. The fruits yielded by this collaboration have included the creation of the first artificial limb (the Utah Arm), the first successful artificial heart transplant, the seeds of the Human Genome project, one of the world's largest and most comprehensive population and health databases, the first real-time cardiovascular monitoring system and, most recently, the 2007 Nobel Prize in Physiology or Medicine.

Currently, two leading Utah organizations – its flagship institution of higher learning, the University of Utah; and its largest indigenous healthcare system, Intermountain Healthcare – are building on the state's storied genetics legacy. This Community Report explores the progress of key initiatives at each of these pioneering institutions.

### **The University of Utah: Moving FURTHER Toward Personalized Healthcare**

With its long-standing strengths in genetics, informatics and model systems, the University of Utah (U of U) brings unique assets to the personalized healthcare enterprise. Credit for this belongs in large part to the Utah citizens, leaders and community partners who have supported genetic research for more than 60 years, when U of U physicians first recognized the power of the state's large families and meticulous genealogical records in studying inherited traits. In 1946, the U of U was awarded the first-ever extramural research grant by what is now the National Institutes of Health (NIH), for "The Study of Metabolic and Hereditary Disorders" in Utah families. Today, Utahns' continued support translates into a greater-than-95-percent participation rate in biomedical research studies – the nation's highest.

One of Utah's leading contributions to modern genetics is the Utah Population Database (UPDB). Established in the mid-1970s through a collaboration between the U of U, the State of Utah and the Church of Jesus Christ of Latter-day Saints (LDS or Mormon Church), the UPDB began as a computerized genealogy file containing demographic and kinship information for more than one million individuals in about 170,000 Utah families. Today's UPDB continues to grow, with data for approximately six million individuals in families that span up to seven generations. Individual records are now linked to other data sets, including Utah birth and death certificates, electronic medical records from the state's major healthcare provider networks, all Utah hospital discharge summaries, and cancer registries from Utah and Idaho.

Analysis of UPDB data led to some of the earliest descriptions of the heritable component of cancer and the identification of major cancer predisposition genes, including BRCA1, BRCA2, p16 and HPC2.<sup>1,2</sup> Current areas of research involving the



UPDB include high-risk pedigree studies of melanoma, prostate cancer, breast cancer, colon cancer, major depression, asthma, influenza, intracranial aneurysms, pelvic organ prolapse and incontinence syndromes, autism and chronic fatigue syndrome.

Concurrent with UPDB work in the 1980s and 1990s, U of U researchers Drs. Mark Skolnick, Ray White, Mark Leppert and Jean-Marc Lalouel were leading efforts to develop molecular markers to map inherited diseases in Utah pedigrees. Within a few years, the power of chromosome mapping methods was demonstrated with the localization of the genes for conditions such as retinoblastoma, cystic fibrosis, neurofibromatosis type 1, several forms of neonatal epilepsy, the inherited colon cancer syndrome and the familial adenomatous polyposis coli syndrome. U of U research into diseases caused by inherited traits continues to the present, with the identification of genes responsible for a variety of neurodegenerative disorders, cardiac ion channel disorders and developmental disorders.

In 1984, Utah played host to a now-legendary event known as “The Alta Summit,” which took place during a blizzard at the Alta ski resort in Utah’s Wasatch Mountains. Sponsored by the U.S. Department of Energy and the International Commission for Protection Against Environmental Mutagens and Carcinogens, the gathering of scientists, including U of U professors Drs. Ray Gesteland and Ray White, focused on measuring heritable mutations in atomic bomb survivors from Hiroshima and Nagasaki. Their conversations generated a flood of ideas and plans that ultimately influenced the design of large-scale genome mapping and sequencing projects – and are now widely credited as the genesis of the Human Genome Project.<sup>3</sup>

Complementing the U of U’s strength in human genetics research are its resources for animal models of human development and disease, including the products of Dr. Mario Capecchi’s pioneering work in mouse gene targeting. This method allows scientists to alter any gene of interest in a single mouse, and from that mouse produce a lineage of animals that pass the mutation – and its effects – from generation to generation. Using these lineages, scientists can assess the effects of disease-causing mutations, determine biological mechanisms and test new therapies. It is fair to say that mouse gene targeting technology changed the way the world does biomedical research. This work earned Dr. Capecchi the 2007 Nobel Prize in Physiology or Medicine and provided the foundation for a host of U of U research programs that use genetically malleable model systems such as nematodes, planaria, zebrafish, fruit flies and newts.

The U of U’s legacy in genetics and model systems, together with its one-of-a-kind population database, position it to make unique and valuable contributions to the discovery science facet of personalized healthcare. In addition, Utah has led key developments in clinical informatics, an area that is crucial to the delivery of personalized healthcare. In the early 1970s, Salt Lake City-based Intermountain Healthcare, with the guidance of U of U medical informatics professor Dr. Homer Warner, implemented one of the nation’s first electronic medical record (EMR) systems. The U of U also participated with the Veteran’s Affairs (VA) Salt Lake City Health Care System and other VA sites in the development of the award-winning VISTA/CPRS electronic health record software.<sup>4</sup> Today the U of U’s Department of Biomedical Informatics (DBMI)

fosters partnerships across Utah's major health care systems to refine EMR and clinical decision support systems, develop new tools and demonstrate their impact on medical care and quality of life.

Like our peer institutions, the U of U is reviewing its portfolio of strengths relative to the numerous challenges in personalized healthcare, and determining next steps in building its programs. We recognize that many of these challenges – data management, regulatory, economic, policy, ethical, education and social issues – can be effectively addressed only through close collaboration with local and national partners. The remainder of this report will focus on how the U of U and its partners are addressing a critical challenge upon which many of our future efforts will rely: Developing a collaborative infrastructure for data integration and delivery across diverse research, clinical and community domains.

While traditional informatics allows us to create the clinical or bioinformatics data infrastructure for a single institution, personalized healthcare requires the integration of disparate research, clinical, and community data both within and across institutions. Above and beyond creating a secure yet accessible informatics infrastructure, this requires rethinking the tools used to process data and the training strategies needed for effective adoption. To be truly integrative, the infrastructure should be scalable – ultimately to a national network of biomedical research centers – while incorporating stringent regulatory and policy implementation strategies. Equally critical is the need for adopting strategies that ensure effective social and cultural change.

To address this challenge, the U of U is spearheading a statewide collaborative, named the Federated Utah Research Translational Health e-Repository (FURTHeR), which will provide the informatics infrastructure for integrative, collaborative, and transformative research. FURTHeR will link genotypic, phenotypic, genealogic, clinical, environmental and public health data from disparate sources statewide and present them through a Web-based portal to patients, community providers and researchers according to appropriate access policies and regulations. It will integrate the substantial research resources within the U of U as well as data from the State of Utah Department of Health and the state's three major healthcare delivery networks (University of Utah Healthcare, Intermountain Healthcare and the VA Salt Lake City health care systems).

Covering more than 85 percent of the state's clinical data and nearly 100 percent of statewide population-based public health data, this remarkable array of phenotypic data will be integrated with the UPDB and enhanced with genotype data as planned biobanks become a reality. The result will be an unparalleled platform for translational training, research, and innovation, one with a special strength in assessing multiple factors – genetic, genealogic, environmental and geographic – that contribute to complex diseases. Designed with scalability and extramural connectivity in mind, FURTHeR employs biomedical and industrial standards while enforcing patient and institutional privacy protections.

THE FURTHeR project has begun with available data resources, and it is growing incrementally as additional systems are incorporated. While it is currently focused on providing research data infrastructure, FURTHeR could eventually contribute to

processes that inform clinical decision support. In a unique first step toward this end, we are working in concert with the National Cancer Institute (NCI) to use some of the basic Cancer Bioinformatics Grid (caBIG)<sup>5</sup> tools and methods in the development of the FURTHeR system.

The repository is “virtual” in the sense that each data source will continue to reside in its home organization, with its own architecture, access policies and procedures. A common road map (meta-model) will describe what is in each system and how to access it. FURTHeR will federate these data using a grid-computing framework<sup>6,7</sup> for resource sharing and a fair-broker data integration service<sup>8</sup> to ensure that data-access policies are enforced among the partners. In Figure 1, the central node, shown in green, will initially provide three key services:

**Metadata integration service.** Using metadata services, FURTHeR will classify and describe data from disparate sources<sup>9</sup> and deliver a consistent data model to the end user.

**Fair broker data access service.** The fair broker service enforces access policies unique to each data source, acting as the final gatekeeper to metadata and data. This is a critical social engineering and regulatory task. At first it will provide security and regulatory compliance during user-initiated data searches. Over time we expect that it will also assist in discovery and ontology management.<sup>10</sup>

**De-identified “data sandbox” service.** In translational science, researchers, policymakers, administrators and other users often need aggregated views of data across institutions, or they need limited views of de-identified data for individuals (i.e., data conforming to the HIPAA Privacy Rule 45 CFR Parts 160, 162, and 164). The FURTHeR “data sandbox” will provide these views, promoting collaboration through comprehensive, statewide access to data. It also provides a powerful educational resource for a variety of courses and programs.

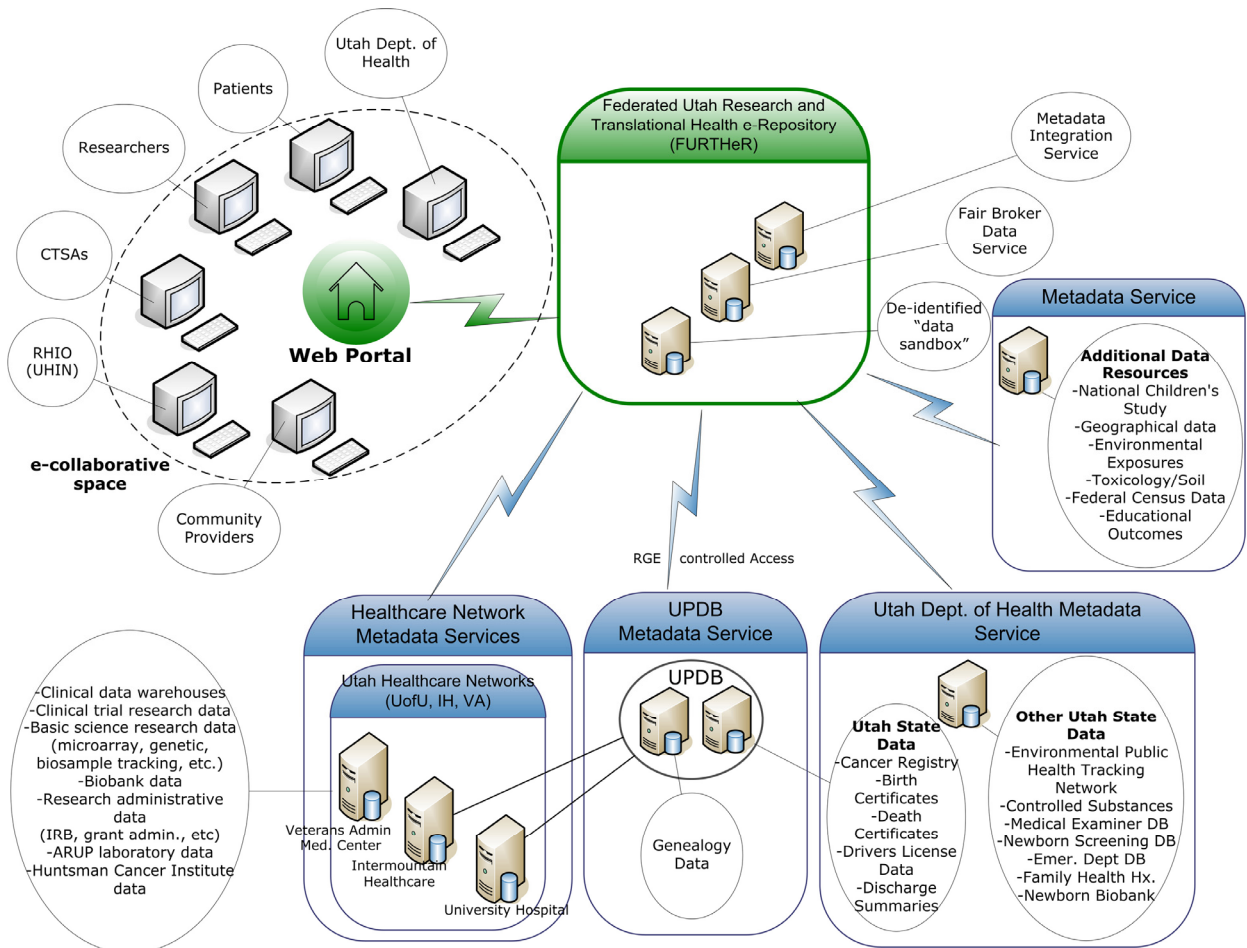
The strategic plan for FURTHeR is ambitious, but its potential for success is bolstered by numerous existing and planned institutional and cross-institutional activities that are being integrated to realize the overall vision. We have a running start with a 50-year history of informatics in Utah, with generous institutional support, and with an extensive set of collaborative projects that have already laid groundwork for the project. Table 1 contains a list of these projects.

In addition, we capitalize on the laws of the State of Utah, which allow for the aggregation of data from multiple sources (with adequate privacy protections) for the purpose of research to enhance the health of the citizens of the state (Utah Code Sections 26-3-7, 26-5-2, 26-25-2, and 63-2-206). The current linkage of data in the UPDB derives from multiple sources, including the Utah Department of Health, the genealogies of the State’s founders, and the electronic medical records of the U of U Health Care System and Intermountain Healthcare. Few states promote (or even allow) this sort of linkage; Utah both promotes and protects them with the power of the law. The U of U has worked within this system for 30 years and has developed a separate review board, the Resource

for Genetic and Epidemiologic Research (RGE), to set and enforce access policies for these data.

The FURTHER project is supported in part by a Clinical and Translational Science Award (CTSA; Public Health Services research grant numbers UL1-RR025764 and C06-RR11234 from the National Center for Research Resources) as well as generous institutional support from the U of U Research Foundation.

**Figure 1. FURTHER Informatics Architecture Overview**



**Table 1. Resources That Contribute to FURTHeR**

Name	Description	Partners
<b>GCRC Core Informatics</b>	Funded since 1964, the U of U General Clinical Research Center has been a leader in CRC informatics. In 1998, at the request of the National Center for Research Resources (NCRR), it organized a team to rewrite the existing NCRR guidelines for the GCRC CDMAS leading to the creation of the GCRC Informatics Cores nationwide.	U of U  National Center for Research Resources (NCRR)
<b>Utah Population Database (UPDB)</b>	The UPDB is the premiere system worldwide for studies that link genomic, phenomic, and genealogical data. Instrumental in the discovery of several cancer-related and other important disease genes, its data cover nearly six million individuals. Recently, Intermountain Healthcare added links to their patient cohort.	U of U  Intermountain Healthcare (IH)  Utah State Department of Health (DoH)
<b>U of U Enterprise Data Warehouse and Information Technology System</b>	This warehouse integrates data from over 200 disparate sources serving the U of U health enterprise, including clinical, research, financial, and administrative data that reach back a decade or more.	U of U
<b>Intermountain Healthcare Enterprise Data Warehouse</b>	Building on the HELP and HELP2 electronic medical record systems, the IH warehouse stores data from 21 inpatient and more than 100 outpatient healthcare sites. Much of the data reach back twenty years or more.	IH
VA VISN 19 Enterprise Data Warehouse	Developed by the local Salt Lake City Veterans Affairs (VA) medical center, this regional warehouse consolidates key clinical data for veterans in Utah, Colorado, Wyoming and eastern Nevada.	VA
<b>Utah Department of Health Data Resources</b>	Many of Utah’s extensive Department of Health data resources have helped to build the UPDB.	DoH
<b>Huntsman Cancer Institute, (U of U) Informatics Shared Resource</b>	This group of provides database, Web, and application development in support of the programs and other shared resources of the Huntsman Cancer Institute (U of U). A formal collaboration with Intermountain Healthcare began in 2006 to examine statewide data.	U of U IH

<b>National Children’s Study Resources</b>	A collaboration between the U of U and IH’s Primary Children’s Medical Center, Utah hosts one of only seven funded NCS study centers, which collect +20-year longitudinal data on children and their families. Popularly called the “Framingham Study” of children, NCS will collect and analyze clinical, genealogy, educational, environmental and genotype data.	IH U of U DoH
<b>ARUP National Reference Laboratory Resources</b>	ARUP is one of the largest national reference laboratories, processing samples from all 50 states daily. A company wholly owned by the U of U, ARUP offers more than 2,000 tests and employs more than 2,000 employees.	U of U IH
<b>U of U Center for High Performance Computing</b>	The CHPC offers a configurable cluster supercomputer with over 1,500 processing nodes; extensive consulting and training services; and experience in grid-based computing.	U of U
ERICA (electronic IRB)	The U of U Institutional Review Board (IRB) has been automated since 2005. Called ERICA, the system supports human research protection for investigators at all three healthcare networks, is itself a research data source; and provides IRB oversight of FURTHeR.	U of U IH VA
Informatics, Decision-support, Evaluation, Analysis and Surveillance Center  <b>(IDEAS Center)</b>	The only VA Health Services Research center devoted to informatics-based research, this collaboration between the VA and U of U facilitates research at the intersection of health services and informatics.	VA U of U
<b>EpiCenter for Prevention of Healthcare-associated Infection</b>	This recently funded CDC “EpiCenter” aims to transform the practice of infection control and healthcare epidemiology through the effective use of health informatics.	U of U VA DoH
CDC Center of Excellence in	Complementing the EpiCenter and the IDEAS Center in their roles as translational	U of U DoH

Public Health Informatics	informatics/health services resources, this Center of Excellence studies how public health can better prepare and respond to communicable disease outbreaks and other public health problems.	
i2b2	The Informatics for Integrating Biology and the Bedside program is an NIH-funded National Center for Biomedical Computing at Harvard University; it works in collaboration with the U of U DBMI to test and implement translational informatics tools.	U of U HU
<b>USTAR Focus Area in Personalized Medicine</b>	One of the core aims of the state-funded Utah Science Technology and Research (USTAR) initiative is to invest heavily in personalized medicine, playing off local strengths in genetics and genealogies.	State of Utah UU
<b>Homer Warner Center for Informatics Research</b>	Intermountain Healthcare, a key partner in the CCTS, has established a center devoted to informatics research, drawing on U of U Department of Biomedical Informatics (DBMI) faculty and IH staff.	IH U of U
<b>Veteran's Affairs (VA) Office of Information and Technology</b>	The Veterans Health Administration (VHA) maintains a small number of large software centers that develop and maintain the code that runs the VHA; one of these centers is located on the SLC-VA campus and, through faculty and former graduates who work there, maintains close ties with the DBMI.	VA
U of U Scientific Computing and Imaging (SCI) Institute	The SCI Institute is a multi-center enterprise, including an NCRN Center for Integrative Biomedical Computing. SCI provides special strengths in tool building and training, with strengths in visual computing.	U of U
<b>Cancer Bioinformatics Grid (caBIG) and Clinical Data Interchange Standards Consortium (CDISC)</b>	DMBI faculty direct local caBIG development and participate in the CDISC Panel of advisors.	U of U  National Cancer Institute (NCI)
<b>Eccles Health</b>	The library leads major community outreach and public health education	U of U DoH

<b><i>Sciences Library</i></b>	projects throughout the State, in addition to serving as the Mid-Continental Regional Medical Library that leads six states in provision of knowledge based services.	VA
<b>U of U Program in Genomic Medicine</b>	An institution-wide program that organizes and supports university and state initiatives to advance genomic medicine in Utah.	U of U
<b>unite.utah.edu</b>	Unite is a secure online knowledge management system that enables university groups and their external partners to collaborate independent of place, time and silo boundaries. With document management, user-controlled workspace customization, Web 2.0/social networking tools, email integration and a contextual search engine, Unite is a growing repository of U of U institutional memory.	U of U
<b>U of U Genetic Science Learning Center / learn.genetics.utah.edu</b>	The U of U Genetic Science Learning Center is a powerful tool for educating public audiences as well as science teachers and students. Its Web site, learn.genetics.utah.edu, is the world's most widely used genetics education resource, receiving more than seven million unique visits per year from people in 160 countries.	U of U NCRR Howard Hughes Medical Institute (HHMI)

### **Intermountain Healthcare and the Clinical Genetics Institute**

Intermountain Healthcare is a not-for-profit health system based in Salt Lake City. Serving the health care needs of Utah and southeastern Idaho residents, Intermountain's system includes 21 hospitals, numerous clinics, a health plan and a physician group of more than 500 practitioners. Intermountain has been named the nation's first- or second-place integrated healthcare system for the past nine years, by *Modern Healthcare* magazine and by the leading healthcare data analytics firm, Verispan. Verispan presents an annual study reporting on its examination of more than 500 health systems around the nation. The annual list rates local and regional healthcare systems on factors such as services and access, technology, hospital utilization and financial stability.

In 2007, the Dartmouth Medical School study found that Medicare spending could be reduced by a third – while maintaining or improving quality – if the nation provided healthcare the way it's provided in the greater Salt Lake City area. The study specifically cited Intermountain Healthcare as an organization that provides high-quality, highly-efficient care. These accolades reflect Intermountain Healthcare's commitment to best



practices that provide a backbone for developing, testing and implementing high-quality, evidence-based personalized medicine with optimal value.

### **Electronic Medical Record (EMR) system**

In partnership with Dr. Homer Warner and the University of Utah's Department of Medical Informatics, Intermountain developed one of the nation's first large EMR systems (see also above in the University of Utah section). The Intermountain electronic data warehouse contains longitudinal medical records on nearly six million individuals, some of which go back more than 30 years. In addition to the electronic storage of information, the informatics system assists physicians with point-of-care clinical decisions for treating diabetes, community-acquired pneumonia, ventilator management, and coronary heart disease. E-resources imbedded in the EMR allow providers access to a wide range of electronic context-specific information sources.

Intermountain Healthcare has been recognized by many outside groups for its innovation in medical informatics. The American Hospital Association's magazine, *Hospitals & Health Networks*, named Intermountain Healthcare in its list of the "Top 100 Most Wired" health care organizations in the country, the Health Information Resource Center awarded Intermountain Healthcare gold, silver, and bronze medals at its 2005 National Health Information Awards and the journal of the American Hospital Association named Intermountain Healthcare one of the nation's most technologically savvy hospital systems for the eighth time in nine years.

### **Quality improvement**

Another critical and unique resource at Intermountain is the Institute for Healthcare Delivery Research, created in 1990 to assist Intermountain in the formal application of quality improvement techniques within the clinical care setting. The approach of Intermountain Healthcare to quality management has been accepted as a national model by the Hospital Research and Education Trust, the research affiliate of the American Hospital Association. Since 1992, the Institute has trained thousands of Intermountain employees and hundreds of physicians and other clinicians from across the United States and around the world in the principles of health care quality improvement.

Intermountain has received top national awards for providing quality health care, including the 1996 NCQHC Quality Health Care Award. *U.S. News & World Report* ranked Intermountain's LDS Hospital as one of America's Best Hospitals in 2006 for orthopedic care, treatment of respiratory disorders, pulmonary medicine, endocrinology or diabetes care, and urology.

### **Intermountain Healthcare's Clinical Genetics Institute (CGI)**

In 2005, after more than three years of strategic planning and in recognition of the increasingly important role that genetics and genomics will play in the future of medicine, Intermountain launched the CGI, which aims "To promote excellence in the quality and value of healthcare throughout our service area by implementing developments in genetics/genomics within Intermountain Healthcare." CGI's values include:

- The belief that genetics/genomics can be a catalyst for a revolution in disease prevention, management and treatment
- The belief that patients and families have the right to understand genetic implications across generations when making health care decisions (personalized medicine)
- The belief that Intermountain can contribute to regional, national, and international development and application of genetics/genomics information into clinical healthcare practices
- The belief that personalized medicine can be realized only through the use of Intermountain Healthcare's strengths in informatics, clinical decision support, quality improvement and evidence-based model care processes.

The CGI will use this mission and these values to address the rapid and dynamic changes anticipated with the addition of genomic information to the existing repertoire of clinical data used in the practice of medicine. CGI staff members have a wide range of expertise, including clinical genetics, genetic counseling, health care delivery, payer issues, education, technology assessment, economic analysis, quality improvement and informatics.

As the largest integrated health system in the Intermountain West (and one of the largest in the country), Intermountain provides a wealth of opportunities to research the effectiveness and value of genetics and genomics in health and disease. One of the most active areas of research is the use of genomic tests to guide the use of drugs that target the products of disease-causing genes.

A significant challenge facing personalized medicine in the future is the ability to put genetic and genomic information in the hands of providers in a useable form at the point of care. The CGI staff serve on several national boards and committees including the American College of Medical Genetics Board of Directors; the Secretary's Advisory Committee for Genetics, Health and Society; the Personalized Health Workgroup of the American Health Information Community (DHHS); Ethics Advisory Group and Billing and Reimbursement Task Force of the National Society of Genetic Counselors; and the Clinical Genomics workgroup of HL7.

Additionally, the CGI has worked closely with the CDC's EGAPP (Evaluation of Genomic Applications in Practice and Prevention) and CETT (Collaboration, Evaluation and Test Translation) programs in order to promote evidence based evaluation of emerging genetic and genomic tests. Dr. Williams is actively promoting incorporation of formal quality improvement methods into clinical genetics by founding the Quality Special Interest Group of the American College of Medical Genetics and spearheading a national quality project through the Mountain States Genetics Regional Collaborative Center (funded by the Health Resources Services Administration-HRSA).

### **Current CGI Projects:**

- **Family History**

With grant support from HRSA through the Genetic Alliance the CGI is exploring ways to increase the use and utility of the family history through integration into the EHR. Specific projects include development of a patient-entered family history form in the patient portal (a web based interface into Intermountain's EMR designed for use by patients). Once created this tool will be studied to see how information could be sent to clinicians as well as providing information for clinical decision support and patient health messages. In 2008 Intermountain Healthcare received a Microsoft HealthVault award to develop a tool for the HealthVault personal health record and explore how the information collected in that tool could be transmitted to EMRs. The CGI has also contracted with the Department of Health and Human Services to provide technical expertise to the DHHS, the Veterans Administration, the Department of Defense and the Indian Health Service to develop a standardized family history collection tool.

- **Genetic Care Delivery**

Comprehensive genetic cancer services are being developed throughout the Intermountain system, and links are being established with similar services provided at the Huntsman Cancer Institute. The CGI is currently partnering with oncology, surgery and pathology to implement a system-wide program to identify patients and family members with Lynch syndrome and its associated increased risk for colorectal and other cancers.

- **Genetics Resources in the EMR**

In conjunction with the University of Utah Department of Biomedical Informatics and Intermountain informatics (see also above in the University of Utah section), genetic information resources (both general and disorder specific) are being integrated into the E-resources of the EMR and linked to infobuttons in the patient problem list that are capable of providing point of care "just-in-time" education for several hundred genetic conditions. As genomic tests emerge into practice, educational resources to support appropriate use and interpretation of these tests will be deployed.

The Secretary of DHHS has championed an interoperable EMR in the United States by 2014. The CGI in conjunction with Intermountain Healthcare's informatics department is working with Harvard Partners Center for Genetics and Genomics to pilot transmission of genetic test results between a laboratory information system and EMR using the HL7 Genetic Variation messaging model, which is being offered as an international standard. We hope to begin working with ARUP a Utah-based national reference laboratory to implement this on a larger scale in the near future.

- **Emerging Genetic Test Evaluation**

CGI has initiated a multidisciplinary Genetic Testing Practice Council to evaluate new genetic tests for clinical utility and to develop methods to support appropriate use of new and existing tests found to have clinical validity and utility, while erecting barriers to discourage the use of tests without an adequate evidence base.

A unique aspect of the CGI is the presence of a full-time analyst to address issues of new technology assessment and cost effectiveness. Partnering with other groups such as the

University of Washington School of Public Health Genomics' pharmacoeconomic faculty, the Institute for Preventive Medicine, CDC, and the Economics of Genetics Technologies Seminars (organized by the Health Economics Research Centre [University of Oxford] and the North West Genetics Knowledge Park [University of Manchester]), the CGI is modifying and applying standard assessment tools within an integrated health care system.

Ultimately, Intermountain's extensive experience in implementing evidence-based medicine in its hospitals and clinics will serve as a foundation in Utah for practicing genomic medicine in all levels of clinical practice. The CGI published a method for rapid assessment of genetic tests, a technique that has been taken up by a national specialty society for an evidence review to support development of a clinical guideline. In addition a paper on the economic implications of pharmacogenomics testing for Warfarin dosing presented at the International Society of Pharmaceutical Outcomes Research meeting in 2008 is currently under review for publication.

These endeavors identify the CGI at Intermountain Healthcare as a national and international leader in evaluation and translation of genetic and genomic medicine which should bring the vision of personalized medicine to reality in clinical practice.

With committed support from the State of Utah – which has identified personalized healthcare as a core component of its Life Science Industry Clusters economic development program – the rigorous, groundbreaking research being performed at the University of Utah and the intensive, innovative clinical work being done at Intermountain Health Care will continue to redefine the parameters and reach of personalized health care far beyond the borders of Utah.

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# **Vanderbilt University** Nashville, Tennessee

## **BioVU: The Vanderbilt DNA Repository**

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The Office of Research at Vanderbilt University Medical Center undertook a strategic planning exercise in 2005, to define priority areas for allocation and investment of resources. The strategic plan identifies three priority areas: therapeutic discovery and translation; public health and healthcare; and personalized health and healthcare. The fundamental premise driving the personalized health and healthcare initiative is that we have reached a point in contemporary biology that a strategy of “one size fits all” fails to recognize individual variability in susceptibility to disease, expression of disease, and beneficial and adverse effects in response to therapies. A major thrust of the program is discovery, with the long term goal of developing platforms for evaluation, delivery, and mining of high dimensional information (such as genomics and proteomics) to demonstrably improve delivery of healthcare (<http://www.vanderbilt.edu/oor/about/strategic-plan12-2005.pdf>). One major component in implementation of this vision has been the creation of a DNA repository, whose development and implementation is described here.

### **History**

The development of priorities within our strategic plan in general, and in the personalized health and healthcare initiative in particular, leverages a range of scientific disciplines in which Vanderbilt has had longstanding investments and recognized national and international expertise. Vanderbilt’s Division of Clinical Pharmacology, established in 1963, is the largest and most successful division of its kind. Science in the division, which was supported by over \$20 million in direct funding from NIH in the last fiscal year, focuses on the very broad question of mechanisms underlying individual variability in response to drug therapy in human subjects. Clinical Pharmacology is administratively and philosophically a Division of both the Departments of Medicine and of Pharmacology. Pharmacology at Vanderbilt includes not only strengths in clinical pharmacology, but also in basic pharmacology and in pharmacoepidemiology. The Division is home to the Vanderbilt’s site in the NIH’s Pharmacogenetics Research Network (PGRN).

A second key resource that leverages our efforts in personalized medicine is a two decade-long investment in bioinformatics and information technology. The Vanderbilt Electronic Health Record (EHR), StarPanel, includes data on 1.7 million subjects over the last 10 years and the clinical environment is near-paperless. StarPanel and the associated electronic order capabilities<sup>1,2</sup> are document-centered and all portions of the system are readily searchable for research and quality control purposes. The EHR also includes extensive point of care ordering capabilities, which have now been licensed to and are being co-developed with McKesson as the Horizon Expert Order (HEO) system; HEO includes delivery of warnings that flag serious drug interactions, or potential dosage errors. Information technology support is provided by faculty and staff in the Bioinformatics Center and in the Department of Biomedical Informatics, which currently includes 57 faculty. In addition to service components, faculty have extensive research activities in areas such as processing large datasets and natural language processing.

A strategic planning effort in the late 1990s identified genetics as a priority area of investment at Vanderbilt. Robust research groups in genetics are now housed in the interdisciplinary Center for Human Genetics Research, as well as in divisions of the Departments of Medicine and Pediatrics. Additional capabilities are key to executing our vision of Personalized Medicine and are in place: these include current and next generation sequencing, extensive core DNA storage and genotyping capacity, and informatics and analysis support.

### **Current Efforts**

**Specific programs:** Individual investigators and groups have extensive and well-funded research programs directly relevant to personalized medicine areas such as HIV pharmacogenetics (Vanderbilt serves as the DNA repository for the AIDS Clinical Trial Group); the Ayers Institute, a philanthropically-supported effort to detect early circulating biomarkers in colon cancer; SPOREs in breast cancer, GI cancer, and lung cancer; and the Pharmacogenetics of Arrhythmia Therapy Program, the Vanderbilt node of the PGRN. These efforts are supported by an extensive series of advanced core resources, notably the DNA storage and analysis capabilities described above as well as one of the largest mass spectrometry centers in the world, with a particular focus on proteomics and on molecular profiling for target discovery. Parallel investments in the other arms of the strategic plan, such as a healthcare economics initiative in the outcomes sector and high throughput screening for new therapeutic in the drug discovery sector complement these capabilities. Thus, the environment at Vanderbilt University Medical Center has been nurtured over decades to position the Medical Center to assume a leadership position in the area of personalized healthcare.

**BioVU:** In 2004, institutional leadership committed to development of a DNA repository with the twin goals of accelerating biologic discovery as well as development and validation of methodologies to evaluate and deliver “omic” discovery to the bedside. The model we developed, now termed BioVU, couples extraction of DNA from discarded blood samples with a de-identified “mirror” image of the Electronic Health Record (StarPanel and associated resources). This mirror image, termed the “synthetic derivative” (SD), in essence allows the discarded samples to be used in a fashion

designated as “non-human subjects” by the federal Office for Human Research Protections (OHRP) guideline of August 2004. Implementation of this unique design required extensive preparatory work, including focus groups and community consultation, and evaluation by the IRB, multiple ethics boards, the Institution’s legal department, and OHRP. The research is designated “non-human subjects”, although the IRB felt that, given the project’s unique scope and nature, continuing oversight was desirable. A key enabling step for the resource was a change in the “consent to treat” form that patients sign every year: this now includes a prominently positioned box, in bold, that allows the patient to “opt out” of DNA collection. Only samples associated with a signed consent to treat form with an empty opt out box are included in the resource. Details describing operation of the resource have been published.<sup>3</sup>

### **Challenges, Plans, Patient Impact**

Advantages and disadvantages of an opt-out approach: There are major advantages to this method of sample accrual. First, samples are acquired from individuals across the healthcare system and not selected for as in a clinical trial. Indeed, it is widely recognized that results from clinical trials may or may not be translatable to practice, given that some sets of patients, such as those with complicated medical histories (especially the elderly), are often not studied. Further, multiple phenotypes are represented. Second, the resource has tremendous advantages of scale: sample accrual currently proceeds at 500-1,000 samples per week: sample accrual began in spring 2007 and the resource held 45,900 samples as of Aug. 25, 2008, making it the largest DNA repository in the country. Third, in order to execute this design, the requirement for de-identification mandated an investment in the broad area of data privacy and security. In addition, the de-identification effort reduces re-identification potential, an increasing concern.

There are some disadvantages to this approach. Because the individuals are de-identified, recontact is not possible. Thus, any need for further information, such as environmental exposure or extensive family history, must be sought through other data collections. Focus groups suggested that the opt out rate would be 3-5% and this, indeed, has been our experience. This resource’s unusual design required an extensive planning and implementation effort, as described above, and also including a number of important milestones, such as development and validation of sample handling and de-identification algorithms.

**Current work:** A fundamental question that we are now addressing is whether healthcare information useful for research can, in fact, be extracted from an EHR. One validation study included genotyping the first 10,000 samples accrued into the resource at several dozen SNP sites, identified and validated in recent genomewide association studies as modulating susceptibility to common diseases. The major challenge here has been development of natural language processing methods to identify cases and controls. An initial evaluation of two dozen SNPs associated with Type II diabetes, atrial fibrillation, rheumatoid arthritis, Crohn’s disease, multiple sclerosis, demonstrates that for each disease, at least one previously validated SNP was replicated in our dataset.<sup>4</sup> This is an extremely important milestone for the resource, since it strongly supports the notion that useful information can be extracted from such “real world” resources. The



National Human Genome Research Institute has launched an initiative to evaluate the utility of EHRs associated with DNA repositories, and Vanderbilt is one of five sites participating in this “eMERGE” Network; as well, Vanderbilt acts as the administrative coordinating center for the Network. The five sites will identify 15,000-18,000 subjects with extensive electronic health records and phenotypes of interest (or controls) for genomewide association. This will not only propel the field forward, but will also provide a very rich dataset on which to explore genotype-phenotype associations within an EHR context (<https://www.mc.vanderbilt.edu/victr/dcc/projects/acc/index.php/About>).

**Plans:** The next step for BioVU is development of capabilities to make the resource available to the Vanderbilt investigative community. This involves the development of web-based interrogation tools, and roll out of data use agreements which include as one provision that all genetic information generated will be redeposited into the Synthetic Derivative. Ultimately, when sufficiently large numbers of patients have been genotyped at large numbers of sites, it may be possible to examine genotype-phenotype associations *in silico* without the need for further genotyping.

**Challenges:** The long term goal of the BioVU project is to develop methods to identify, validate, and then implement on a clinical level new high dimensional information. Our current vision suggests that point of care delivery systems such as next-generation HEO will include delivery of increasingly patient-specific warnings and prescribing advice. There are multiple challenges that will have to be overcome for such a future tense vision is executed: What technology to use? How to evaluate the added benefit of integration of patient specific information into healthcare? At what costs? What sort of effect would be deemed “real”? We recognize these and multiple other challenges in the implementation of a next generation personalized healthcare delivery system, and consider BioVU as a key enabling step for studies to address these challenges.

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# National Summit: Summary



**National Summit on Personalized Healthcare  
Convened by Utah Governor Jon M. Huntsman  
October 5-7, 2008  
Deer Valley, UT**

**Introduction**

The 2008 National Summit on Personalized Healthcare, convened by Utah Governor Jon Huntsman, Jr., was held October 5-7 in Deer Valley, Utah. This invitation-only Summit brought together leading stakeholders with varying interests but with shared common goals to engage in a high-level discussion aimed at developing a shared vision of making personalized healthcare a living reality. But beyond developing this shared vision, the Summit took on the mission of identifying specific major barriers to this vision and creating an action plan that the Summit participants and other stakeholders will take to overcome these barriers and realize the shared vision.

The Summit was organized to achieve a common understanding of the possible future for healthcare, especially based on the use of new tools of genomics, molecular diagnostics and informatics. The objectives of the Summit were:

- To create strategies and action plans to accelerate the integration of Personalized Healthcare into clinical practice and healthcare delivery.
- To develop effective strategies to capitalize on the disruptive innovation characteristics of Personalized Healthcare.
- To identify methods and incentives that enable providers to optimize outcomes on both an individual basis and population basis.

Underlying this Summit was the realization that proponents of personalized healthcare have not sufficiently demonstrated the potential benefits in terms of science and informatics, clinical utility, and cost-effectiveness. Achieving these benefits may depend on new approaches in valuation, coverage, and reimbursement and may require new levels of sharing across a healthcare system that is distinguished by the degree of independence of its many separate elements. These represent substantial (and interacting) challenges.

This facilitated meeting began with an evening session that focused on the experiences of 10 pioneering “communities” and early adopters of Personalized Healthcare throughout the United States. The next morning’s opening remarks by Governor Huntsman, Health and Human Services Secretary Michael Leavitt, and Clayton Christensen of Harvard Business School, were followed by a lively panel discussion that offered a vision for personalized healthcare. After two lunchtime keynote addresses by Senator Robert Bennett (R-UT), and Dr. Christensen, the participants worked in small groups to identify and prioritize barriers to integrating Personalized Healthcare in clinical practice. They then organized themselves into five working groups that developed strategies, actions and

milestones to overcome these barriers. The Summit continued the following morning with comments from Senator Orin Hatch (R-UT), a long-time supporter of personalized healthcare, and then moved on to hear reports from the five working groups. The meeting concluded with comments from panels on the action plans that these working groups developed. (This report will focus on the discussions and presentations beginning with the first full day of the Summit. Details on the Community Reports are elsewhere in this volume.)

The 2008 Summit, the first of a planned annual event, took place at an inflection point for both personalized healthcare and for our larger national healthcare system. It examined the real gaps in knowledge that still exist, the extent of work yet to be done, and the systemic characteristics that threaten to render personalized healthcare a failed or deferred promise. By the time the Summit ended, the participants had developed a series of joint actions and strategies that they and other stakeholders can take to accelerate the application of personalized healthcare in clinical practice.

### **Opening Remarks**

Governor Huntsman opened the working sessions by reminding the Summit participants that there is much at stake for the nation regarding efforts to reform healthcare and making personalized healthcare an integral part of any reforms efforts. Successful reform will make healthcare a powerful engine of economic growth, while failure will have severe, multi-trillion dollar consequences for the U.S. economy. It is his hope, he said, that this inaugural Summit would become to healthcare reform what the Davos meeting has become to the world economy.

Secretary Leavitt seconded Governor Huntsman's comments and provided some chilling statistics to drive home the importance of the Summit's work. In the early 1950s, healthcare spending accounted for 4 percent of GDP. Today, that figure stands at 16.5 percent and is heading to 25 percent of GDP. That dramatic increase has resulted from the fact that our nation's medical system today focuses on volume, not value. Reversing this trend demands great science, but also the application of the science to improve the value proposition so that our reimbursement system rewards those medical practices that work, rather than those that move large numbers of patients through the system.

Finally, Dr. Christensen noted that the central problem the nation is facing - that healthcare is going to become impossibly expensive – is not unique to healthcare. Indeed, almost all new industries, including higher education and the automobile, telecommunications, and computer industries, started off being too expensive and too complicated, but each of these industries made the transition into something that was simpler, and more affordable and accessible. Their path from expensive and complex to affordable and simple involved disruptive innovation. And in each case, disruptive innovation required three things to happen:

- Technological breakthrough(s) that changed a problem from complex to simple
- Technology that simplified this problem became embedded in a business model

- That business model had to be connected intimately with a supply chain and business network that could make this happen.

He then drew a parallel between the chemical industry and the healthcare industry. In the years after World War II, there were perhaps 50 people in the world who were skilled enough to work out new ways to synthesize chemicals, and DuPont employed virtually all of them and as a result dominated the industry. However, as chemists practiced their craft, they derived rules that enabled an average chemist to become skilled in the arts of chemical synthesis. Scientific progress commoditized this expertise, rather than replicated it. Healthcare today is where DuPont was 60 years ago. The body's vocabulary of physical symptoms isn't large enough to be specific for all diseases, and as a result, too many diseases have very similar symptoms. This leads to too much trial and error, which requires a high-level of expertise, or intuitive medicine. Dr. Christensen then said that this situation will change only when technology transforms the ability to diagnose and recommend care, to make it less intuitive and more rules-based. The process of developing the technologies needed to take healthcare in this direction are coming, and this is quite exciting. However, he cautioned, the U.S. doesn't yet have a business model or a delivery system in place to enact this model effectively, efficiently, and in a value-driven, cost-effective manner.

In the ensuing open discussion, speakers made the following points that were germane to the day's deliberations:

- There is a critical need for standards by which to judge value.
- The most direct impact of personalized healthcare will come with the development of specific, accurate diagnostics that will lead to more appropriate therapy with higher value and lower cost.
- Today's healthcare system involves a tradeoff between quality and cost, but personalized healthcare should be the technical enabler to eliminate this tradeoff.
- The most efficient path for a disruptive technology is to address simple problems first, not the most difficult. For example, the first widespread commercial use of transistors was in cheap pocket radios, not expensive televisions.
- An integrated healthcare system profits from keeping patients healthy instead of treating them when they become ill.

### **Vision For Personalized Healthcare Expert Panel And Discussion**

Following a break, the meeting facilitator, Robert Mittman, convened a panel discussion with Ralph Snyderman, Chancellor Emeritus for Health Affairs at Duke University; Mara Aspinall of Genzyme and Harvard Medical School; and Brent Wallace, Chief Medical Officer of Intermountain Healthcare. Dr. Snyderman made the point that the major problem facing healthcare today is in the delivery of acute treatment for late-stage chronic disease. As a result, personalized healthcare, with its emphasis on early detection guiding value-driven, effective therapy, can serve as the disruptive technology that can effectively address this problem. He noted, however, that developing the predictive diagnostic tools to accomplish this task represents a huge scientific challenge, though once such tools are available, healthcare will not only become personalized, but

predictive and participatory, with the doctor-client relationship becoming more of a partnership in which the patient and doctor will develop a wellness plan in response to the physician's more knowledgeable assessment of that patient's risk for certain diseases.

Dr. Aspinall continued with the statement that personalized healthcare will need new rules and economics, but if it works well it will save lives and can't help but save money. The evidence that this approach will work can be found in the way HIV infection and some cancers, particularly hematological cancers, are now treated. Today, for example, we know that there are more than 90 different types of leukemia and lymphoma, and diagnosis and therapy have become highly individualized. As a result, survival rates have gone from virtually zero to as high as 90% with many of these blood cancers.

The problem is getting full adoption of this model, which she sees as a three-step process of fear, followed by realization of value, and then true adoption. Today, we are in the fear stage, where the pharmaceutical industry says that markets will be too small to justify the research investment needed to develop personalized diagnostics and therapies and where payers believe that personalized healthcare will be too expensive. Moving to the value phase will require development of data-driven anecdotes showing that personalized medicine is value-driven. Getting adoption to occur will require changes in medical education, the development of a robust information technology infrastructure revolving around electronic medical records, and a reimbursement system that is based on value, not volume.

Dr. Wallace noted the dire need for large-scale, population-based research, which will require an improved consent process so that data gathered during the delivery of healthcare can be consolidated for research. Today, he noted, there are too many incompatible data systems and there is no good system for sharing data across systems. There is also a need for a new information technology-based educational system for physicians that would push new information out to physicians in a way that they will both accept and use new data as it becomes available. Dr. Wallace commented, too, that intellectual property issues must not be overlooked in any discussion about how to push new scientific advances into medical practice.

Important points raised during the subsequent discussion included:

- Physician societies can play a critical, enabling role in "retraining" physicians regarding personalized healthcare, but they will need to speak with a unified vision.
- For purposes of reimbursement, diagnosis and therapy need to be thought of as two parts of a whole, not two separate entities. Keeping them in separate silos for reimbursement purposes makes it difficult to draw an accurate picture of total costs versus total benefits.
- Patient education will play a prominent role in the acceptance of personalized healthcare given that patients will need to become more involved in managing their own health portfolios as medical practice transitions from one of treatment of illness to one of maintenance of wellness.

- There is a critical need for evidence-based clinical trials, including Federal support for these trials, that will examine how genomic information relates to early detection of disease and identification of predispositions for specific diseases.
- There is the expectation that technology is delivering the disease markers needed to make personalized healthcare a reality, whereas in fact, this is a very difficult scientific challenge. Today, most of the genetic risk factors that have been identified account for less than half the risk for a particular disease, and indeed, we are still in the early phase of discovery in terms of using genomics, proteomics, expression profiling, metabolomics, and other new data-driven techniques to identify predictive disease-related information.

### **Lunch Speakers**

Utah Senator Robert Bennett began a short lunchtime talk with a comment that recent national surveys show that Salt Lake City is one of the three best places in the U.S. to get health care, and yet healthcare costs in Salt Lake City are 1/3 less than the national average, in large part because of the better integration of the entire healthcare system that has taken place in Salt Lake City. The senator then discussed the Healthy Americans Act that he and Senator Ron Widen (D-OR) are co-sponsoring. The Healthy Americans Act aims to break the link between the employer and the healthcare system. The person who is making the expenditure – the company – is the same as the person receiving the service – the employee or a family member. The core principles of the Healthy Americans Act include:

- Everyone has to be covered – the system won't work if people can stay out because those in the system carry the freight for those who aren't covered. This is an individual mandate. Senator Bennett noted that Republicans have to give up their resistance to this idea.
- Control of healthcare dollars rests in the hands of the individual in the form of a Health Savings Account with standards. The senator commented that Democrats have to give up their resistance to this idea.
- All health insurance is portable, an idea on which both Democrats and Republicans agree.
- The best way to control costs is to make better use of great medicine. Rewarding healthy behavior through incentives, including lowered premiums as people get healthier, and rewarding those practitioners who keep their patients healthier, are necessary to successfully reform the nation's healthcare system.

Next, Dr. Christiansen discussed in more details his findings on disruptive technologies. Disruptive innovation, he explained, creates asymmetric competition. Every market has an ability to utilize improvement, and every market has a different trajectory that companies take. However, the pace of technological progress occurs faster than the market has the capacity to absorb. Making a new technology that is affordable and simple creates new markets with new planes of competition. Dr. Christiansen's research has found that whenever these disruptions occur, there are three enablers:

- Simplifying technology that commoditizes expertise.



- Business model innovation to deliver that simplified technology in an affordable manner.
- New value network develops with suppliers that are willing to participate in these new markets.

One reason why personalized healthcare has not had much impact on medical practice yet is that the field has not yet developed this business model and the new network with which to distribute personalized healthcare.

What is a business model and how is it built? Dr. Christensen explained that a good business plan always starts with a value proposition – a product that helps customers to do more effectively, conveniently and affordably a job they’ve been trying to do. Next, the business model develops the resources and processes needed to deliver this value proposition to the targeted customers. The final piece of the business model is the profit formula that dictates the value proposition. The key regarding disruptive technologies is that they destroy current business models and require the development of an entirely new business model. As an example, he said that today’s hospitals operate on a horrific business model that would not be viable except for the fact that the reimbursement system is set up to maintain this model. Therefore, for personalized healthcare to make an impact on the nation’s medical and fiscal health, this model will have to be destroyed and replaced by a new model that is still being developed. As an example of a new business model, Dr. Christensen cited National Jewish Health in Denver, which has improved the successful treatment of patients with asthma and other respiratory diseases by developing an integrated care model focused on a patient-specific wellness plan.

### **Barriers and Underleveraged Resources**

Following lunch, Summit participants gathered in small groups to identify barriers that are impeding the development and dissemination of personalized healthcare. The barriers, which served as fodder for the subsequent development of action plans, included:

- Capital constraints
- Lack of awareness about personalized healthcare among the general community
- Gap between scientific understanding and patient care; the rapidly changing biomedical knowledge base is difficult to incorporate into updated clinical practice
- Intellectual property issues relating to gene patents
- Difficulty obtaining regulatory approvals for disruptive biomedical technologies resulting from a lack of understanding among regulators
- Lack of a reimbursement process for medical innovations and disruptive technologies
- No payment system at the Centers for Medicare and Medicaid Services (CMS) to reimburse for molecular diagnostics
- Delinking of the consumer, payer, and provider
- Genetic and genomic knowledge relating to clinical outcome is missing –does value exist when these markers are used in a real clinical setting? The data doesn’t exist yet to guide physician action.

- Paying for volume (fee for service) rather than fee for outcome.
- Failure to reimburse for preventive medicine
- Fragmented or siloed research and development
- Fragmented or siloed healthcare delivery
- Human nature, which leads to non-compliance, little appreciation for preventive actions and life-style changes, and inaccurate risk perceptions among the general public
- Cost and inefficiencies in research and development for therapeutics
- Zero risk tolerance - the expectation of perfection is not achievable, and what we have to live with is relative risk – inhibits the development of improved therapies that offer a substantial benefit over existing therapeutics, but that are still not perfect, i.e., the search for perfection inhibits development
- Uncertainty in the regulatory area make it difficult to attract investor interest
- Uncertainty in the reimbursement area make it difficult to attract investor interest
- No fully dedicated diagnostics division at FDA or CMS.
- There is no good mechanism for bringing combination diagnostic/therapeutic solutions through the FDA approval process
- Our systems are not sufficiently adaptive to reward value across a continuum.
- The introduction of innovation into the system is difficult in a rigid system
- There is insufficient ability to manage medical information in an information-rich world
- Antiquated and legacy models of disease based on organ systems and histology
- Total inability in terms of time, money to generate rigorous outcome data for personalized medicine. Everyone wants evidence, but we don't have the ability to generate it.
- For clinical trial resources, there's a scarcity and fragmentation and lack of coordination making it difficult to test new therapies appropriately
- Lack of reimbursement for early adopters
- Business models for payers, providers, and patients are often at cross purposes
- Inefficient use of infrastructure – under-utilized capacity in this country.
- There is a need on the one hand for openness in data sharing in research and development, but also closeness because of the claims of privacy and property rights
- We don't know how to generate, execute, and evaluate a trial that can identify low-response therapies that will nonetheless benefit certain groups of people
- We need an educational system that trains healthcare providers in a way that works with personalized healthcare
- Lack of an understanding about cultural beliefs regarding medicine – population diversity and a need to develop approaches that recognize this
- There is no financial incentives for doctors to use electronic medical health records

Once this list was generated, the participants then divided themselves into five groups that tackled one or more of these barriers and generated a game plan of specific action items that could overcome the selected barriers. The five working groups were set up to examine the identified barriers from the perspective of business, science, delivery of services, people, and Utah's emerging personalized healthcare industry and infrastructure. The results of these deliberations were presented to the Summit the

following morning following brief remarks from Utah Senator Orrin Hatch on the need to reform Medicare and Medicaid.

### **Business Perspective Report**

This group began its discussion on the premise that it was important to set a relatively short time frame to accomplish realistic goals, rather than setting long-term, lofty goals that might never be realized. With that perspective, the business group set as its primary objective the goal of creating commercial incentives to encourage the adoption of targeted approaches to healthcare that improve the efficiency and value of healthcare outcomes. The group's members intend to reach their goal within two years and to have quarterly accomplishments that they will be able to report on at next year's Summit.

In the immediate term, the group intends to create a task force to develop a new reimbursement framework for diagnostics and to develop a framework to support the creation of a diagnostics division at FDA. Over the two-year time frame, the group intends to develop case studies demonstrating the value proposition that can drive adoption of personalized health care by stakeholders. These case studies will focus on diagnostics, the role of healthcare information technologies, and on successful business models. The Personalized Medicine Coalition, whose representatives were part of this working group, is already working on these case studies. In addition, this group intends to develop of definition of personalized medicine that will emphasize its role as an enabler of broader access to healthcare and as a powerful force for cost reduction. This definition will then serve as a foundation for a common language that the field can use in making its case for the adoption of personalized healthcare as a key component of healthcare reform.

This team also identified several metrics by which to judge its success, including:

- personalized medicine becomes part of the healthcare reform agenda;
- the group identifies and engages key opinion leaders in its efforts;
- the group forms teams that develops detailed action plans for meeting its goals in the two-year time frame, including a plan to engage regulatory and legislative bodies; and
- the group develops working financial models for personalized healthcare.

One key to success for this working group will lie in its ability to engage and leverage the work of existing coalitions.

### **Science Perspective Report**

The science working group developed two primary objectives. Its first objective is to develop a roadmap for compiling the data needed to support adoption of personalized healthcare. This roadmap will be based on explicit scientific principles of evidence needed to demonstrate and understand the benefits of a personalized healthcare approach to medical practice and on explicit standards of economic benefit. To accomplish this goal, the science team will first develop a consensus group to identify elements that need to be incorporated into this road map and to establish stratification criteria based on risk

and perhaps on new definitions of disease based on molecular criteria. The roadmap will also include a strategy for establishing a stepwise approach to acceptance that will build from easy-to-document cases, and to aid that effort, the team will also identify various sources of supportive data that may already exist. Building on this evidence, the working group will strive to validate findings and then work to gain traction among the payer and provider communities. On a cautionary note, this team said that its efforts must always be patient-centered and clinically relevant.

Measures of success include the development of appropriate financial models and incentives that can be used to garner stakeholder support and the development of a strategy for educating thought leaders about how to judge data showing the benefits of personalized healthcare. Another metric of success will be the identification of places for quick wins and then moving to develop actionable pilot programs with well-defined objectives and buy-in that will mobilize stakeholders to participate in these pilot programs.

The science working group's second goal is to create a clinical decision support system tied to health information technology and built around a core of phenotypic molecular data. The first task will be to establish a consensus group that will identify key elements, ontologies, and standards for a fully integrated distributed information technology module designed to assist in the clinical decision-making process using up-to-date data. A second task is to identify sources of evidence, whether it be in the form of data from randomized clinical trials, existing registries, databases or networks such as the National Cancer Institute's caBIG<sup>®</sup>, the National Cardiovascular Data Registry, and the FDA's Voluntary Genomic Data Submissions database. In addition, this team intends to develop pilot programs for implementing this information technology module in a clinical care setting. This team plans to hold a joint workshop in July 2009 with whitepapers from each of the two sub-teams and to have a full report ready for the October 2009 Summit.

### **Delivery Perspective Report**

This working group based its discussions on the premise that data must follow a patient through the healthcare system if the goal is to achieve the best possible outcome for that patient. It therefore set as its primary objectives the development of a set of case studies of how an integrated, portable electronic medical record combined with an information technology module that codifies evidence-based practice rules improves health outcomes while reducing costs. The group identified three specific examples involving efforts in breast cancer, diabetes, and cardiac care that it will use to develop these case studies. The team aims to use the data from these three examples to generate outcomes data that will support policy change and to look at what types of incentives would dovetail with these outcomes data in a way that would encourage adoption of this type of fully integrated system. This working group noted that it may also want to look at examples outside of a medical setting, such as the wellness initiative established by IBM for its employees. To meet this objective, this group needs to recruit champions to push these findings among the various stakeholders, an effort that will require the development of an integrated communications plan and engagement of patient groups. This group plans to work with the Personalize Medicine Coalition to identify potential champions and to leverage ongoing efforts by the Coalition and other interested parties.

### **People Perspective Report**

The primary objective of this team is to develop a comprehensive communications strategy designed to educate the various stakeholders in the healthcare reform debate. This strategy will be centered around patients in order to empower them and to reinforce the message that the success of healthcare reform depends on a patient-centered, personalized healthcare approach. To achieve this objective, this group developed a set of tasks that will begin with creating a two-way dialog with patient groups that will identify patient needs that reflect differences in language and culture. As part of this dialog, the group intends to develop a set of definitions and common language that can be used to unify patients behind a banner of personalized healthcare. This effort would also include creating a Web site – MyPersonalizedMedicine.com was suggested – that would enable patients to aggregate their medical information in one place. Such a Web site would also include various patient-education modules, such as one that could simulate, based on specific medical information, how various actions on the part of the patient would influence their health on a short-term and long-term basis. This team also intends to identify incentives and actions that would drive patients to such a Web site and encourage its frequent use, i.e., to make the use of such a Web site become mainstream, a part of modern life. Recruiting national figures such as Oprah Winfrey and the community of television writers to become involved in this effort is paramount to success, which will ultimately be judged based on measures of increased patient involvement in their own healthcare.

### **Utah Community Perspective Report**

This group's primary objective is to build on Utah's leadership in gene discovery and diagnostics and on an existing infrastructure recognized as providing the highest quality patient care at the lowest necessary cost to make Utah a leader in personalized healthcare. Achieving this objective will require breaking down the silos and fragmentation that exists even in the fairly well-integrated Utah healthcare system and overcoming the distrust that exists among stakeholders based on past bad experiences. The first action that this group will take is to convene a group that will own this vision, work to integrate the various expertises available in Utah, and identify expertise that is missing but that could help drive this effort. The group may consider recommending that Utah create a personalized healthcare "czar," that would coordinate and oversee these efforts. At the same time, this group will connect with the already-established Utah Healthcare Task Force to see how these efforts can be coordinated. This working group will also convene a meeting of Utah scientists who may be interested in these issues in order to develop a scientific vision of what personalized medicine means and how it can be disseminated throughout the Utah healthcare system. This group of scientists could also serve as a marketing tool, both within and outside of the state.

This working group also noted that there are some issues that are beyond its control, namely competition, cooperation, collaboration, and collusion; this latter issue has arisen previously in Utah. This group acknowledged that it needs to be mindful of state and national regulations in this regard, particularly concerning data-sharing and patient privacy. This group also intends to develop methods of measuring the value of personalized medicine for the state's industries in terms of reduced healthcare costs and improved worker health.

### **Closing Roundtable**

Following the working group reports, Mr. Mittman convened a roundtable discussion with Elias Zerhouni, outgoing director of the National Institutes of Health; Peter Traber, president and CEO of the Baylor College of medicine; and Raju Kucherlapati, scientific director of the Center for Genetics and Genomics at Partners HealthCare. Dr. Zerhouni started the conversation by noting that personalized medicine suffers from what he termed from multiple personality disorder, and the clarification that occurred at the Summit represents a necessary step towards the successful integration of personalized healthcare into the medical system. He noted that the Summit's participants must now undertake a huge effort at conveying what they have done and to drive home the message that personalized healthcare sits at the apex of what fundamentally is more precise medicine, and thus better medicine. Dr. Zerhouni also reiterated the message that perfection is not the goal, but that improved patient-centric care with reduced costs is the goal. Keeping that in mind, the field should aim to develop personalized medicine in stages, focusing first on therapeutics because that is where the greatest impact will be. Diagnostics, which will depend on still-developing science, should be the next target, followed by the development of more accurate predictive medicine. Each of these steps is going to require its own roadmap to success.

Dr. Traber said that he comes away from the Summit both excited by the prospects of personalized healthcare, but unsettled by the many different views of what personalized healthcare means. There is a real need, he noted, for an overarching vision that can unify many constituencies, and most importantly, focus on value to the patient. One important point that came across in this Summit is that personalized healthcare brings science home to the individual, yet science is foreign to the vast majority of the population of the United States. This represents a real challenge to the field, but it also represents an enormous opportunity to link science to an individual's genome, medication, and wellness. He also commented that it is clear that personalized healthcare needs to be intimately involved in overall healthcare reform and encouraged the Summit's participants to find ways to sit at the healthcare reform table. At the same time, the Summit discussions made it clear that the medical community must be brought into these discussions immediately in order to start what will be the difficult task of getting enthusiastic acceptance of the key concepts of modern personalized medicine.

Dr. Kucherlapati then exhorted the Summit to follow through on the action plans they developed. He suggested that the Personalized Medicine Coalition could serve as a national organization that would oversee these efforts and keep them on track. He also recommended reaching out to executives in the biotechnology industry, a stakeholder that will undoubtedly play a major role in developing the tools for personalized healthcare and that can help speed the translation of laboratory findings into clinically useful tools. As an example, he cited the collaboration between his laboratory and Genzyme Genetics that will result, starting in January 2009, in all patients at Partners HealthCare with non-small cell lung cancer being tested for specific genetic variants prior to the commencement of therapy.

## **Final Thoughts**

To end the meeting, Mr. Mittman asked John Glaser, chief information officer of Partners HealthCare; Carol Kovac, managing director of Burrill & Co.; Steve Prescott, president of the Oklahoma Medical Research Foundation, Ray Gesteland of the Eccles Institute of Human Genetics at the University of Utah; and Dr. Christensen to provide some closing comments. Dr. Glaser noted that information technology is central to personalized healthcare and that the Summit teams need to learn more about the many ongoing initiatives at the state and Federal level that could play into this field and to form partnerships with the groups that are overseeing these initiatives. He stressed that no one group can tackle this issue, so building partnerships with other stakeholders and groups outside of the central core of healthcare reform is a critical endeavor that must happen sooner rather than later. He reminded everyone that the goal is not to be disruptive just for the sake of disruption, but rather the goal must be to advance the practice of medicine, perhaps through the adoption of disruptive technology.

Dr. Glaser also introduced a note of caution, reminding the participants that there is still very hard science to do in order to generate the data needed to fully implement personalized healthcare based on molecular diagnostics. Yes, he said, the field should be encouraged by what is happening in the cancer field, but it is also important to remember that common, chronic diseases account for the majority of healthcare spending and that these will be the hardest challenges to tackle.

Dr. Kovac recommended that the Summit participants keep Dr. Christensen's comments about disruptive technology in mind as these efforts progress. Specifically, she said that the field should be actively searching for low-hanging fruit as a pragmatic way of making progress, but at the same time, the field must not overlook the big, paradigm-changing developments. Efforts that strive for the latter may fail, but the ones that succeed will be the transformative ideas and technologies that make personalized healthcare a reality. She also said that there is a place for the venture capital community to play a role in these efforts, particularly in terms of looking at the bigger picture of what technology can be put together with the right business model and partners to create solutions that patients and payers. She also stressed that the public sector needs to continue funding the science and clinical work that will ultimately prove the value proposition that lies at the heart of personalized healthcare. And in a final remark, she stressed that the field needs to rally around existing coalitions, and asked the Summit participants to consider creating a master map of the actors in this world. Having that master map would lead to strategies that target the key players and accelerate progress in this field.

Dr. Prescott said that he would leave this meeting adopting a broader view of personalized healthcare that is part and parcel of healthcare reform. It is clear, he said, that there is a real need for new business models that reflect the known benefits of personalized healthcare, while also engaging government to become a more active player in this field. He was also struck by the fact that efforts should already be underway to integrate every individual's personal data because this task will only become more difficult as more molecular information becomes available.

Dr. Christensen provided the final comments by reiterating that going after the simple things is critical. The challenge will be that the thought leaders in the field are involved in solving the most difficult problems, so it is important to keep the simple things front and center. He closed his remarks by noting four common errors people commit in terms of promoting good theory:

People are so anxious to describe what needs to be done that they don't describe the measure of what the phenomena really are. He noted that he does not see that happening in this field.

There really is value in a common language, and there must be compromise to develop that language.

Sometimes we view the discovery of an anomaly as a failure of theory, but this is wrong – anomalies provide the opportunity to explore what information outliers are providing. Most bodies of understanding accumulate in an ad hoc, disjointed way, and there can be great value in setting up an organization and journal to be a repository of the best thinking, which in turn, speeds the eventual adoption of theory.

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