Personalized Health Care:
Opportunities, Pathways, Resources

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PERSONALIZED HEALTH CARE: OPPORTUNITIES, PATHWAYS, RESOURCES

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FOREWORD

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In the coming years, new gene-based knowledge, combined with the advent of health information technology, can make possible a new kind of medical care for Americans: Personalized Health Care.

Of course, health care professionals have always aimed at making medical care as individualized as possible. But in truth, our ability to deliver the right care for each person has been limited.

We have had only partial understanding of human biology at the molecular and genetic levels, where each of us is biologically unique. Our understanding of each person's particular susceptibility to diseases, as well as his or her individual responses to therapies, has been limited. Physicians diagnose and treat on the basis of symptoms that can be seen and felt. But they have not had access to the underlying biological processes, unique to each of us, that start with the "instructions" in our genes.

At the same time, even our systems for using the health care information that we possess have remained paper-based and siloed. Patient records, filed in different settings, can be difficult to access – a poor foundation for personalization of care.

Finally, we have yet to use the power of networked information that has transformed many other sectors. Despite growing complexity in health care, there is limited online support at the bedside to help health care professionals deliver the best standard of care for each patient. In addition, while controlled clinical trials remain the staple of progress in biomedical science, the additional wealth of information that might be reaped from millions of encounters in day-to-day medical practice remains untapped.

This is not to say that the progress made by American medicine has been anything but remarkable. But the opportunities that present themselves today hold the possibility of a transformation over the coming years and decades that is even more far-reaching. It involves not only breakthroughs in scientific knowledge but, equally important, the application of this knowledge on a patient-by-patient basis. We can see the possibility of health care that is increasingly calibrated to each patient and personally effective for each individual.

One part of the foundation for such a change is our rapidly growing understanding of the human genome and the processes it directs. We envision health care that could:

- predict our individual susceptibility to disease, based on genetic and other factors;
- provide more useful and person-specific tools for preventing disease, based on that knowledge of individual susceptibility;
- detect the onset of disease at the earliest moments, based on newly discovered chemical markers that arise from changes at the molecular level;
- preempt the progression of disease, as a result of early detection; and
- target medicines and dosages more precisely and safely to each patient, on the basis of genetic and other personal factors in individual response to drugs.

Another part of the foundation for personalized health care is the potential for health information technology to help develop new knowledge and put it to effective use. When health information exists in electronic form, capable of being shared securely, it can:

- make the patient's complete health information available when and where needed;
- provide support to clinicians when they need it, to help them give patients the best standard of care, including information based on individual genetic and molecular factors;
- through secure networks, bring together masses of data from day-to-day medical practice to accelerate our understanding of which treatments work best, and to monitor for safety problems in real time; and
- use the medical evidence developed from such networks to understand differences in patients' response to drugs and other therapies, learning who benefits from specific treatments, so that therapies can be targeted on a more individualized basis.

Personalized health care is information-based health care. It is health care that works better for each patient, based partly on scientific information that is new and partly on technology to make complex information useful. Whether it involves new biomedical knowledge, data networks for developing that knowledge, or computer supports to manage that knowledge, personalized health care is about a transformed role for information in health care.

This report is an early "reconnoitering," a glimpse from the perspective of the Department of Health and Human Services (HHS) of the work that lies ahead to achieve personalized health care. From this early stage, we can outline the opportunity. We can roughly see the building plan and identify some of the key elements and pathways that must be traversed. We can recognize the importance of collaboration. We can identify broad prerequisites for personalized health care. And we can identify the HHS resources that are already in play.

We can also identify the need for standards in many new areas. More broadly, we can see the imperative for collaboration across the private and public sectors and across many disciplines and stakeholders.

Finally, 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 health care possible. In addition to developing the information, we must use it correctly.

One of my priorities as HHS Secretary is to help build a strong foundation for personalized health care. That means coordinating work across HHS agencies as well as addressing crosscutting issues, to ensure that new information and capabilities will be used appropriately.

We cannot entirely foresee how different health care may be in the coming decades. It seems inevitable that there will be a significant period of disruption and learning as new capabilities are developed and adopted. Nonetheless, it is incumbent on us to take steps now, even as basic knowledge and technologies are being developed, to anticipate and enable that future. The goal of the health care professional remains to deliver the right care to the right patient at the right time, and that is what personalized health care is about.

Personalized health care means knowing what works, knowing why it works, knowing who it works for, and applying that knowledge for patients. These goals may sound elementary, but a generation of effort lies before us in achieving them – perhaps one of the most complex science-based endeavors in our history. We approach it with high hopes and humility.

OPPORTUNITIES

Envisioning a New Kind of Health Care

The potential of science to relieve human illness and suffering has long captured people's hearts and imaginations. In the quest to realize that promise, funding from public, nonprofit, and private sectors converged in the 1980s, boosting the budgets for biomedical research beyond that of engineering and the physical sciences for the first time ever. Fueled by a budget that has nearly tripled in the last decade, biomedical research has become an engine that is now driving the health care system toward new frontiers.

The rate of growth has been exponential. Indeed, for more than 1,000 years, physicians had to rely upon what they could see, palpate, or intuit in order to diagnose, treat, and monitor patients. The last 100 years have brought deeper understanding, as researchers moved from the macroscopic to the microscopic level, learning of cells and cellular processes and fashioning tools and treatments born of these findings. The most recent decade broke all records. Systems biology, bioengineering, genomics, proteomics, nanotechnology, cellular and tissue engineering, bioimaging, computational methods, and advances in information technologies have all shuttled medicine into a molecular future at a pace that exceeds people's ability to fathom it.

Looking Through a Medical Prism: Disease by Disease

Looking back, we can gain perspective on how far and how quickly we have come.

In 1940, physicians identified cancer by the tissues in which it resided and had access to few treatment options, except for surgery and medications with poorly tolerated side effects. Oncologists today are redefining cancer as the interplay of faulty genes and proteins, independent of tissue location. These are linked to biochemical pathways that are already providing "targets" for custom-designed, cocktail-style therapies.

Physicians in 1940 would not have known to counsel patients with potential heart disease about cholesterol and the risks of high-fat diets and high blood pressure. Often the first symptom of heart disease was sudden death. Now physicians view heart disease as a probability that can be reduced or prevented through knowledge of risk factors, changes in lifestyle, screening exams, medication, and surgical techniques.

Likewise, physicians in 1940 saw diabetes as a pronouncement of a short, restricted, and complication-plagued life. By contrast, contemporary physicians view diabetes as a disease to be managed over a patient's long lifetime. Doctors today can offer their patients knowledge about its cause, tests for early detection, effective medications, and more sophisticated blood sugar monitoring devices.

And further, today, through clinical and health services research, we know that the progression of diabetes and cardiovascular disease may be significantly influenced by addictive diseases and depression, and that addictions may be a risk factor for some types of cancer. Current brain studies and research into the genetics and biological markers for substance use disorders have the potential to render care even more effective for conditions that are affected by substance abuse.

Personalized Health Care: The Culmination of Biotechnical and Medical Advances

As testimony to medicine's swift progress and wide-scale success, people are living longer and healthier. While this is an event for celebration, it also presents other issues. Currently 13 percent of the U.S. population is older than 65 years. In the next 25 years, that number is expected to increase to 20 percent. As the population ages, we can expect its risk for diabetes, heart disease, cancer, Alzheimer's, and other diseases, associated with mid to later life, to rise in tandem. Thus, America's health system is now shifting to accommodate an older population prone to have complex illnesses caused by multiple factors.

Basic research advances in the context of these changing clinical imperatives have brought a signal point of transition. We anticipate an era of personalized health care. This is the shape of health care in the future: a system that is patient-centric and enables patients to make choices about their health management, with enhanced quality and safety.

Personalized health care is envisioned as a system in which doctors, pharmacists, and other health care providers customize treatment and management plans for individuals. It will be founded upon vast amounts of information that will be readily accessible at clinics and hospital bedsides. The driver is the many applications of information technology that have blossomed during the biomedical revolution. For example, tools like electronic capture will allow easy dissemination and flow of data about medical history, genetic variability, and even patient preferences. Patients will ultimately receive this information, specifically as it applies to them.

This is already happening. A woman with breast cancer now has the option of a predictive test that tells her whether her tumor bears a genetic signature. If she tests positive for the overproduction of a gene product called human epidermal growth factor 2 (HER-2), she is a good candidate for a companion drug called Herceptin, which reins in her excess HER-2 and nearly halves her risk of disease recurrence.

Similarly, a patient with chronic myelogenous leukemia (CML) has access to a diagnostic test that indicates the presence of a mutant gene, called Bcr-Abl. If a patient tests positive, he or she can take a drug called Gleevec, which binds specifically to the faulty gene's product and so inhibits its cancer-causing action. Early studies show a 90 percent initial response rate in patients with CML and the hope of complete remission.

Personalized health care also offers the potential of gauging a person's unique drug metabolism. In the doctor's office, a patient can get a test that discerns whether he or she has a particular combination of 31 possible genetic variations in two liver enzymes, known as cytochrome P450, which together are responsible for metabolizing 40-45 percent of all drugs. The test is intended to help physicians fine tune dosage, based on molecular metabolism rather than previous crude weight estimation.

At its core, personalized health care opens the door to a future focused on disease prevention. This is best demonstrated by a current test for a woman's predisposition for breast cancer. If she has certain BRCA1 or BRCA2 gene variations, she bears a higher lifetime risk of breast and ovarian cancer. A woman in this situation has the choice of increasing preventive measures, including mammography and clinical breast exams, ultrasound imaging, and biomarker detection. She may also choose to be more aggressive, opting for prophylactic surgery that removes at-risk tissue and/or chemoprevention through drugs such as tamoxifen.

Personalized Health Care Becomes the Norm: The Implications

HER-2, cytochrome P450, and other examples are special cases, but they represent first instances of personalized health care at work. Over time, such cases will amass until they reach a tipping point, when personalized health care becomes the norm rather than the anecdote. As that happens, personalized health care must involve the innovative application of such tools and the knowledge of how best to use them.

The key players in this transformation are health care providers. With new tools, doctors will play new roles. Where once physicians had to practice medicine much like an art form, using macroscopic tools to alleviate symptoms, personalized health care will provide molecular tools and information technology support to deliver care with greater precision, confidence, and individualization.

Making use of genomic profiling tests, large databases of predisposing factors, sophisticated monitoring devices that provide data in real time, and streamlined electronic patient records, physicians will better prevent disease, predict outcomes, and help patients heal faster through personalized care. Doctors also will have electronic tools that give real-time updates about, for example, drug contraindications and results of improved post-surveillance monitoring methods. With these aids, doctors will not have to waste time gathering redundant information. Rather, "smart" tools will enable physicians and nurses to use their time with patients more effectively and to better present choices of treatment and the implications that will follow.

This paves the way for a new doctor-patient relationship. Patients can have access to better communication tools. Interactive systems will allow patients to query electronically about health choices. Patients will have the opportunity to become more health literate and take more responsibility for their own health care. Experiencing fewer side effects and better efficacy of treatment, patients will be more likely to engage in their personalized treatment and management plans. They will be better enabled to view themselves as in control of their own health care. As such, they may be increasingly interested in assembling their own health care information, including individual genetic profiles, family history, past treatments, even personal preferences, into health portfolios – analogous to financial portfolios – to be managed with the help of health care planners, managers, and coaches. Doctors will be better positioned to work with teams of health care service providers who contribute and interpret complex information so they can better guide patients in their choices.

Health care providers, meanwhile, will be making changes of their own. With better screening and profiling tools, medicine can increasingly shift from a reactive and disease-focused model to a health maintenance and preventive care approach. Health care providers will have the ability to track patients through always-current electronic "charts," available when needed for treatment. This will eliminate the need for repeated collection of histories and physicals, therefore saving time and cost.

Drug developers of the future may also see a cheaper, faster, safer system of discovery, development, and delivery. The current "linear" pipeline of product development should bend into a more "circular" channel. By making de-identified clinical information available on a large scale, the day-to-day delivery of health care can become a platform for research, as well as for quality and safety improvement. When large volumes of aggregated clinical data (stripped of personal identifiers) are available in real time, new avenues will be open to researchers for discovering better leads, more quickly and more closely in tune with real patient needs.

At the same time, with better molecular profiling tools, drug developers will also have the capacity to better tailor their treatment and screening technologies toward smaller numbers of patients. This means that pharmaceutical innovators will be enabled to move away from the blockbuster, one-size-fits-all approach. Instead, "mini-busters" can be targeted to well-identified subpopulations.

Finally, drug approval regulators will develop better models of clinical testing that are coupled with biomonitoring systems which track patients in real time. Overall, development will also shift toward

prevention, including early diagnostic indicators as demand for such products increases in tune with patient and physician demand.

This vision of a new kind of health care rests on the achievements of the past, the gathering speed of advances in biomedicine and information technology, and decades of further work. But if the past is prologue to the future, we can expect the investment of time, talent, and resources to grow steadily and the speed of change to be rapid. Converging biomedical technology, medical practice, demographics, and policy initiatives offer a new vehicle to drive personalized health care forward.

CHALLENGES

Prerequisites to Achieving Personalized Health Care

Some important crosscutting social, legal, and technical issues which are prerequisites for achieving personalized health care include the following:

Public Trust

The introduction of powerful genomic technologies into the health marketplace has the ability to positively impact us as individuals and as a society. Genomic information has unique potential to identify and predict the health outcomes of individuals and their families. Establishing the public's trust for use of personal health and genetic information in electronic health care management systems will be key to ensuring public acceptance of new medical genetic technologies.

An overarching principle of personalized health care is that an individual's predictive genetic information, when acquired for health care purposes, should be used only for health-related activities, and should not be used inappropriately in making employment or health insurance coverage decisions.

Genetic and Molecular Research

Building on the success of the Human Genome Project, research will emphasize characterizations of the genetic basis of disease and better understandings about the interdependence of genetic and environmental factors. Advances in our basic understanding of research results are bringing the scientific meaning of disease to new frontiers for clinical application. Using powerful consortia of research organizations, biomarkers (specific biological traits used to measure the progress of a disease or treatment) are being identified to better identify the biological underpinnings of specific pathologies.

Some of our research, development, and medical product review processes are focused on more effective, targeted therapies. This knowledge is being translated into clinical tests to monitor drug therapy, thereby enabling health care providers to select drugs that work safely for specific patients and conditions. To ensure widespread adoption of this important new technology, we need to ensure that medical genetic test information is both clinically and analytically valid.

Translation of Knowledge Into Clinical Practice

Rapid advances in technology, biomedical research, and medicine often take many years to be adopted throughout the health care delivery system. The rapid rate of scientific and medical advances outstrips the ability of clinicians and providers to remain up-to-date on the latest medical information. We need better and more efficient ways to provide useful information to support clinical decisions of health care providers and consumers. The lack of user-friendly information sources often hampers adoption of newer approaches, such as the incorporation of genetic testing practices in routine clinical decision-making.

To support the readiness of health professionals and change clinical practice patterns to reflect best practices, robust clinical decision support and information management tools will need to be integrated into electronic health records and other health information technology systems. New provider education in the use of genomic information is also likely to be needed.

Underlying improvement in the translation of advances into health care delivery and the adoption of best practices is the need for strong medical evidence. Personalized health care must be strongly aligned with the development and use of evidence-based care. At the same time, adoption of new tests, therapies, and techniques will be strongly affected by evidence of their clinical and economic value. The development of medical evidence focused on patient outcomes, and the ability to compare alternatives, will be an

increasingly important element of health care. The development of systems for developing evidence from the health care delivery can add significantly to the evidence base and to growing knowledge of individual variations in response to treatments.

New Processes and Relationships in Product Development

New demands on medical product review will point toward improved integration of government and industry roles and responsibilities. The relationship of industry and academia in basic research and development will continue to undergo change driven by shared responsibilities in technology development and genomic applications reflected in funding methods and intellectual property management. In the short term, this will be manifested by shared support of research projects to validate technological approaches to assess molecular, genetic, and imaging parameters in medical product development. Agreements for sharing precompetitive data (especially meaning broadly applicable findings developed through cooperative processes, or otherwise made available for use without patent exclusivity) among public and private entities, particularly of genomic databases, will broaden discovery opportunities, enhance safety assessment, and diminish investment risks in targeted molecular therapies and diagnostics. Additionally, new dynamics may emerge in employer/employee relationships in supporting personalized health care programs through incentives and Web-based information tools.

As the health care system focuses on disease prevention and preemption through personalized approaches based on risk assessments, these advances will drive a need for new reimbursement strategies and other incentives. Personalized health care disease management approaches will be evidence-based. The advancements in health information technology, improvements in standardized phenotypic characterization of disease parameters, and increased understanding of unique biological factors responsible for individual differences in health and disease will lead to more informative clinical trial data. Over the next decade, the effects of these steps will result in better information about what works for which patient, which will not only strengthen measures of quality of care, but also improve efficiency in new product development and evaluation. An achievable objective for the future is a richer science and information base that will maximize opportunities for clinical development of new technologies.

Health Information Technology and Knowledge Management

Underpinning personalized health care is the confluence of two powerful tools: information technology and knowledge management. These forces will provide individualized health care know-how at an unprecedented level. The full potential of these forces cannot be realized unless electronic systems, clinical databases, and knowledge repositories employ interoperable standards and definitions.

While innovation in technology to collect information is a key step, data collection alone will not support personalized health care. As technological capabilities develop across the health care system, better information based on individual differences will aid in future medical product evaluations and postmarketing assessments of safety and efficacy.

There is an increasing need for, and value placed upon, integrated datasets and higher quality information about efficacy and safety outcomes. Using integrated databases, the ability to assimilate and relate experiences is enabling new predictive power for outcomes in disease management. Until now, this could only be modeled at a population level. Personalized health care should equate not only with an emphasis on more effective health outcomes but also with prevention and safer health interventions. These interoperable systems and networks will improve the practice of medical care and the health of the consumer and drive increased adoption of these important new technologies.

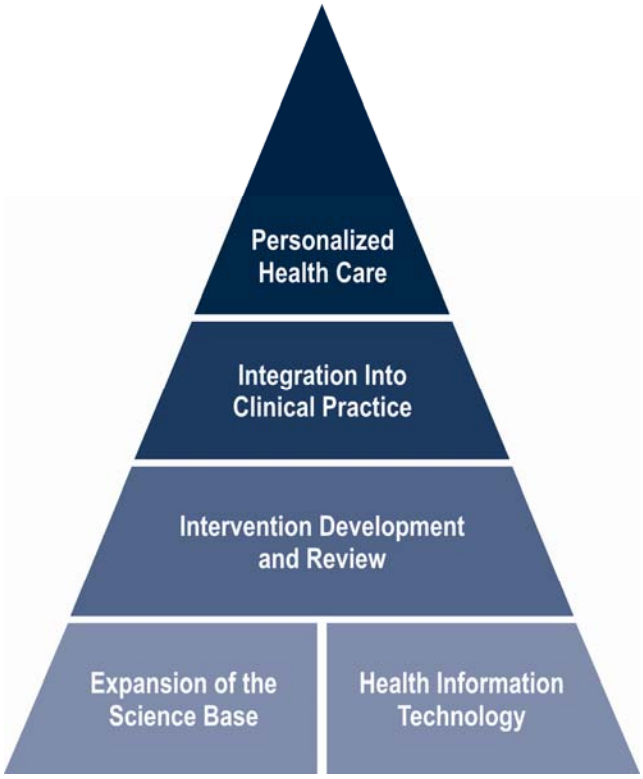
PATHWAYS

Building Blocks of Personalized Health Care

The achievement of personalized health care (PHC) rests on a dual foundation: the growing base of biomedical knowledge (especially related to genomic knowledge) and the adoption of interoperable health information technology.

To this foundation must be added the development of clinically useful products. In order to achieve that goal, appropriate regulatory structures will be needed to support innovation and adoption of safe and effective drugs, diagnostics, and procedures.

Finally, integrating personalized health care into clinical practice will depend on the development of medical evidence demonstrating that these approaches work for clinicians and patients. It will also depend on education and support for health care professionals to translate new knowledge into clinically useful procedures.



Expansion of the Science Base

The Human Genome Project has been successfully completed, and work is continuing to explore the next steps. That work includes learning about the complex biological interactions that result in health and disease conditions, as well as the interactions between genetic factors and our environment and lifestyles. Some salient elements include:

- Continued genome sequencing and mapping: Building on the foundational work of the Human Genome Project, projects continue to refine our understanding of genetic structure and functions. An important example is The Cancer Genome Atlas, a comprehensive effort to understand the molecular basis of cancer. *(NIH)*

- Genome-wide association studies: These studies are a kind of medical detective work, matching the genetic profiles of large numbers of patients in clinical trials with their health conditions. These associations can help uncover patterns that point toward the roles of different genetic elements in health and disease. *(NIH)*

- Genes and environment: The complex relationship between genetics and environmental factors, including factors like nutrition and physical activity, help determine each person's health. The Genes, Environment and Health Initiative *(NIH)* and the Human Genome Epidemiology Network *(CDC)* are early efforts in understanding this relationship.

- Population genetics: To help make genetic information useful, it is important to know the prevalence of genetic mutations and other factors in the population. This information can also be useful in targeting public health activities. Existing health surveys are used to compile this information. *(CDC, HRSA, NIH)*

- The "Omics": Extensive work is needed to understand molecular biological elements beyond the focus on DNA and RNA. In particular, research is needed regarding proteomics, metabolomics, and epigenetics. *(NIH)*

- Computational biology: With 3 billion DNA base pairs and 20,000 active genes in each individual's genetic makeup, development of information is dependent on sophisticated computing power. The computing tools needed for genetic and molecular biology research are in a constant state of invention. *(NIH)*

- Biomarker identification: Chemical and other markers that indicate specific biological activities can provide useful tools for clinical diagnosis and treatment as well as help to speed product development. A public/private Biomarkers Consortium has been formed to help identify useful biomarkers. *(FDA, NIH)*

Health Information Technology

Personalizing health care depends on interoperable health information technology. Health IT can make patient information available when and where it is needed. Health informatics can also help clinicians manage complex information and deliver "best practice" care.

- Technical standards and policies: The American Health Information Community (AHIC) is a Federal advisory committee chartered to make recommendations to the Secretary of HHS on how to accelerate the development and adoption of health information technology, including harmonization of health IT standards. Personalized health care starts with electronic health records that make complete and current patient information available when needed. *(ONC)*

- Genetic information in electronic health records: AHIC's Personalized Health Care Workgroup is developing recommendations for the AHIC on standards for the future incorporation of personal genetic information in an electronic health record, including standards for family history. *(ONC)*

- Confidentiality, privacy, and security: AHIC's Confidentiality, Privacy, and Security Workgroup is charged to make recommendations regarding the protection of personal health information in order to secure trust and support interoperable electronic health information exchange. *(ONC, OCR, CMS)*

- Clinical decision support: AHIC will recommend to the Secretary common elements for using electronic data technologies to support doctors, nurses, and hospitals in delivering high-quality care. *(ONC)*

- "Learning" health care: By aggregating large amounts of de-identified patient data from day-to-day medical practice, researchers can monitor safety and add rapidly to the evidence about what treatments work best and for whom. Combined with controlled clinical trials, this "learning" from practice through health IT can add significantly to effectiveness in health care. *(AHRQ, CMS)*

- Informatics and nomenclature: Deriving useful information from health care delivery will require standardization in measures and nomenclature, as well as sophisticated computer programming. *(NIH, ONC)*

- Quality improvement and health IT adoption: Demonstrations of health IT in a variety of health care settings will measure the impact on quality of care and the dynamics of health IT adoption in real-world situations. *(AHRQ, HRSA)*

Intervention Development and Review

Personalized health care should result in more effective drugs aimed at narrower populations, as well as a more prominent role for diagnostic tests and for co-development of diagnostic and drug products. Regulatory guidance is being developed to support effective development of drugs, diagnostics, and other tools aimed at smaller populations and more precise disease conditions.

- "Critical Path": The Critical Path Initiative has identified 76 scientific and regulatory areas where progress is needed to improve and expand the science base for medical product development. Critical Path enables collaborations with other agencies, regulated industry, and interested public and private health care organizations in building the science base for improved regulation. *(FDA)*

- Submission of genomic data: New and voluntary approaches for submission of data, as well as other guidance for innovators in the field of personalized health care products, are being developed. *(FDA, CDC, NIH)*

- Evaluation of genetic tests: FDA is working to facilitate the development of the in vitro diagnostics that will be utilized in personalized health care, and CMS is carrying out its action plan for oversight of genetic testing. *(FDA, CMS, AHRQ)*

- Pharmacogenomics: Individuals respond differently to drugs. The use of personal genetic information in prescribing the optimal medications for each patient is a promising area of personalized health care. Pharmaceutical developers are encouraged to voluntarily submit genetic data with new drug applications to help learn more about this potential. Clinical research studies are also under way with specific drugs, notably the widely used anticoagulant warfarin, which involves sensitive dosing decisions. *(FDA, NIH, AHRQ)*

- Bioinformatics: Computer modeling may help predict drug effectiveness and safety, including effects on individuals based on genetic factors. Successful modeling could help accelerate drug development and review. *(FDA, NIH)*

Integration Into Clinical Practice

The adoption of scientific advances into clinical practice has typically been slow. New genetic elements will pose additional challenges for health care providers. An important element for achieving personalized health care will be support for clinicians in delivering high-quality care to every patient, including appropriate use of new genomic-based approaches.

- Evidence-based practice: With health IT data networks, health care can increasingly be based on broad evidence of effectiveness. For gene-based tests and therapies in particular, evidence from clinical practice can supplement the narrower data developed in formal trials and thus give clinicians stronger evidence for adopting these approaches. *(AHRQ, CMS)*

- Provider and consumer education: New medical tools will be useful only if they are trusted and used by health care professionals and patients. Communities and professional groups will need to be engaged in learning new practices. CaBIG, the Cancer Biomedical Informatics Grid, is a leading example, linking researchers, patients, and physicians throughout the cancer community to learn new practices and feed back into research. *(NIH, HRSA, AHRQ)*

- Knowledge management and decision support tools: An important element of health IT will be clinical decision support to help providers deliver "the right care to the right person at the right time." Knowledge management tools will also play a part in delivery of more complex care based on genetic testing and therapy. *(ONC, AHRQ, HRSA)*

- Effective use of genetic tests: More than 1,000 genetic tests are now available, but clinicians and consumers need support in determining the appropriate and effective use of such tests. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project is a potential model for providing needed guidance. *(CDC, CMS, FDA, AHRQ, HRSA)*

- Family history: Collection of family history information can be a powerful early tool for improving care and building the base for personalized health care. *(CDC, NHGRI, ONC, Office of the Surgeon General)*

- Costs and reimbursement: The value delivered by new personalized health care products will need to be demonstrated and evidence of effectiveness shown. New approaches in rewarding high quality and value through reimbursement techniques are being tried. *(CMS)*

The Importance of Collaboration

In any scientific endeavor today, collaboration is important. For personalized health care, it is at the heart of the project. Collaboration among different stakeholders, and across public and private sector lines, is not merely key to achieving the goal, it is the essence of the goal itself. "Personalizing" health care means aligning resources across the health sector, from the researcher and the regulator to the clinic and the payer, so that their efforts converge and adjust for each patient. Patient-centric care depends on collaboration for the patient's benefit.

Standards

The concept of using gene-based factors and health information technology together to personalize health care is at an early stage. As we build the foundation, it is especially important to agree on standards in order to create common interfaces, measurements, and vocabularies. Standards are essential both for collaboration in building a system, and for enabling future value-enhancing competition.

Data and technical standards are critical to the advancement of the national health IT agenda and achieving the intended health goals and outcomes. By harmonizing standards, different information systems, networks, and software applications will be able to "speak the same language" and work together technically to manage and use consistent, accurate, and useful health information for providers and consumers. For this reason, harmonizing interoperability standards is a priority for the Secretary of HHS, and with the advice of the American Health Information Community, the Secretary will continue to recognize interoperability standards.

Standards of performance are also important in nourishing a market for health IT. When providers invest in health IT, they need to have measures to demonstrate the value of their purchase. With AHIC's guidance, the Secretary recognized a number of performance standards for health IT systems last year that were then incorporated into the process by which health IT products and systems are certified by the Certification Commission for Health Information Technology.

Standards are equally important in research. An important challenge in seeking out the associations between genetic factors and health will be standard nomenclatures, especially for health and disease conditions. An early start has been made with SNOMED, a broad collaborative effort carried out with HHS support to establish a standardized vocabulary of clinical and pathology terms. NIH, FDA and other agencies continue to bring together stakeholders for extensive further work in these areas.

Agreements on nomenclature and standards for *outcome measurement* will also be important as we seek to use data from clinical practice to add to our base of evidence about the effectiveness of treatments and to improve quality of care.

These are only a few examples of collaborative efforts that are under way to build the base of standards that will help accumulate information, transform information into knowledge, improve care, and create new value.

Translation and Teamwork

Our health care system has historically been slow in translating research advances or even adopting simple quality-improving techniques into daily clinical practice. To successfully adopt "best practices," including quality-driven variations in care between individuals, we will need collaboration at two levels. First, lines of communication among researchers and clinicians need to be open and active. Perhaps more important, strong collaborative "teamwork" approaches in health care settings themselves can make the greatest difference in patient safety and quality of care. Changes in the culture of clinical settings to enable measurement of outcomes and make care more patient-centric can take time and effort, but they are also an important part of personalizing health care.

Building a "Learning" System in Health Care

Doctors and researchers have always learned from their care delivery, but only a few health care institutions have systematically gathered data from patient encounters over time to help determine which treatments are most effective and for whom. Interoperable health IT can make it possible to reap this kind of learning from the broad terrain of day-to-day clinical practice. This approach would depend on cooperation among entities that possess patient data, including their agreement on effective protections for privacy of personal data. In the end, it would actually represent a "collaboration" by patients in a systemwide process of health data development. Large amounts of de-identified patient data from normal health care delivery would become a platform for discovery – a resource for research and a tool for improved safety and quality of care.

The Patient as Participant

Patients are typically seen as the recipients of care. An important ideal of personalized health care is to better enable patients themselves to be participants and guides in their own health care. This is not simply a matter of encouraging personal responsibility for making healthy choices, or becoming more actively involved in choices based on personal preferences or value. More fundamentally, as genomic and other factors give each of us an increasingly distinct and unique health profile, it is hoped that a sense of ownership and personal expertise will grow. Patients will increasingly possess both the information and the sense of authority that will help them become partners in their own care, helped by professionals who are increasingly seen as advisors and "coaches."

Secretary's Initiative in Personalized Health Care:

Using Information Correctly

Genomic information and health information technology both convey new power. As we seek to use that power to improve care and health, we need to exercise the wisdom and discretion to avoid *misusing* it. In the end, the usefulness of these advances will depend on public trust. That trust must be fostered and protected.

A starting point is to avoid misusing genetic information to deny employment or health insurance to individuals. While genetic discrimination has not emerged as a significant problem at this time, surveys show that Americans are concerned about the possibilities for abuse in the future, and they want protections put in place. The Administration supports Federal law to prohibit such misuses.

A leading objective throughout HHS agencies is to build a strong foundation for personalized health care. HHS Secretary Michael Leavitt has launched a PHC initiative, with several cross-cutting elements:

- The President's budget for 2008 includes $15 million in startup funding to create a new electronic network that would draw together data from major health data repositories. This distributed network would be a prototype for a "learning health care system." De-identified data from day-to-day health care practice would enable researchers to add to our base of medical evidence on effectiveness and safety of alternative treatments.

- The American Health Information Community (AHIC) is charged with developing recommendations for consensus standards and other actions that would support President Bush's goal of electronic health records for most Americans by 2014. This year, the AHIC has also formed a new workgroup to develop recommendations for the AHIC on standards for including genetic test information and family history in electronic health records.

- Efforts are under way in HHS to consider issues relating to the use of genetic test information to improve quality of health care within the framework of providing protections for the patient's privacy.

- As a result of the advances in technology development and increased medical knowledge about the roles of genes in health and disease, greater use of genetic tests in health care is anticipated. To prepare for this, HHS is also examining opportunities to help facilitate medical product development and encourage innovation, while taking into account potential processes to assess safe and effective health care applications. The goal is to ensure a coherent framework across HHS agencies and to support value and innovation in genetic testing applications in health care.

- Many new research projects are establishing databases of genomic information from clinical studies. HHS is working to maximize the benefits that derive from federally sponsored research resources by considering common approaches for the availability of their data to the research community.

These steps represent a systems strategy. They are aimed at building a foundation that will use new methods of genetic analysis to better manage a patient's disease or predisposition to a disease, while at the same time facilitating the discovery and testing of new products. They emphasize the development of standards to derive the greatest possible benefit as health information technology brings about exchange of health information, including better bridges between research and health care delivery.

The end goal is to transform the effectiveness of treatments provided for each patient, while building understanding and trust among providers and patients in a new kind of health care.

RESOURCES

HHS Programs Supporting Personalized Health Care

The Department of Health and Human Services (HHS) coordinates a wide variety of programs and projects that support information development, technology, infrastructure, delivery of care, and other resources that promote health and well-being of Americans. Inventoried here are key HHS-supported programs that can serve as resources and building blocks for personalized health care (PHC). In addition to these, there are many other HHS programs and activities that support individualized health care, through outcomes research, health services research, prevention programs, clinical trials, and population health programs.

I. Expansion of the Science Base

Human Genomics Research

National Human Genome Research Institute, National Institutes of Health
http://www.genome.gov/

Description

The National Human Genome Research Institute's (NHGRI's) predecessor, the National Center for Human Genome Research (NCHGR), was established in 1989 for the purpose of leading NIH's component of the Human Genome Project, the international, public effort to sequence all 3 billion DNA base pairs of the human genetic blueprint. The Human Genome Project was completed in April 2003, under budget and ahead of schedule. In January, the National Human Genome Research Institute celebrated its 10th anniversary as an Institute of the National Institutes of Health (NIH), marking a decade that saw genomics emerge as a powerful research tool and looking ahead to an era in which genomics will transform medical care

Status and Next Steps

- During its first 7 years, NCHGR devoted much of its energy to developing the technologies and techniques needed to map and ultimately sequence the human genome. Because the public Human Genome Project placed all the resulting data in freely available, public databases, the sequence of the human genome became available for anyone to use anywhere in the world to conduct medical research and advance the cause of human health.
- NHGRI's Genome Sequencing Program is responsible for the administration and support of research directed to the highly efficient construction of physical maps, large-scale sequencing, and genomic resource production for entire genomes.
- The Human Genome Project quickly showed that humans are more than 99 percent identical at the genetic level; that is, the order of genetic letters As, Ts, Cs, and Gs is almost precisely the same between any two individuals. Researchers also realized that the 0.1 percent genetic difference between people – where a genetic single letter is different – may hold the key to why some are more susceptible to a disease, such as cancer or a mental illness, than someone else. Such inherited genetic differences, or variations, may well explain why diseases, such as diabetes, run in families. Researchers call single-letter differences SNPs and estimate that 10 million would need to be evaluated to predict disease risk, a prohibitively high number of differences if 10 millionSNPs

had to be tested in every individual. Later studies showed that only some 500,000 SNPs needed to be tested across the genome to assess a person's genetic variation. These technical advances led researchers to organize the International HapMap Project, a coordinated effort to map genetic variation in populations of people from Africa, Asia, and Europe. The HapMap produced a catalog of common variations across the entire human genome that has been used to quickly and cheaply assess all the common variants in an individual. This capability laid the foundation for genome-wide association studies to identify the genetic underpinnings of common illnesses (described later). See http://www.hapmap.org/.

- But even acquiring the sequence of the human genome and starting to understand genetic variation were only the first steps in understanding how the human genome works; researchers now need to understand what it does and how it works. Estimates suggested that only a few percent of the human genome actually encoded proteins, the workhorses of the living cells that make up the body. To begin to understand the genome's dynamism, The NHGRI launched a public research consortium named ENCODE (http://www.genome.gov/10005107), the Encyclopedia Of DNA Elements, in September 2003, to carry out a project to identify all functional elements in the human genome sequence. The project is being conducted in three phases: a pilot project phase, a technology development phase, and a planned production phase. Major findings from the pilot project were published in two scientific journals, *Nature* and *Genome Research,* in mid-June; details can be found at http://genome.gov/25521622.

- Since 1990, NHGRI has been investing funds to develop and improve DNA sequencing technologies. DNA sequencing costs have fallen dramatically, more than fiftyfold over the past decade. The goal of this technology development program is to reduce the cost of sequencing a human-sized genome to $1,000. Several new NHGRI-supported technologies aimed at an intermediate goal of $100,000 per genome are now reaching the market place and others show strong potential to become commercially available within the next 5 years. Beyond the intermediate goal, another set of investigators are being supported to develop revolutionary technologies to sequence a human genome extremely inexpensively (conveniently referred to as the "$1,000 genome"). Having the ability to sequence an individual genome so inexpensively would not only dramatically stimulate biomedical research, but would also support personalized health care goals. Researchers envision a day when anyone can have his or her genome sequenced, one time, as part of routine medical care and have access to it in some digital form, such as on a CD-ROM or a flash memory card. Physicians would then use a computer to screen that individual genome for genetically increased risks to common disease, such as cancer or diabetes, as well as use that information to predict which medical interventions will best work to prevent the disease from occurring, treat it effectively if it does, and select therapies that cause the fewest unwanted adverse reactions or side effects. In many ways, these technical genome-sequencing innovations will be needed to make personalized health care economically feasible for all.

Genome-Wide Association Studies

National Institutes of Health
http://grants.nih.gov/grants/gwas/index.htm

Description

The NIH is advancing a series of research initiatives known as genome-wide association studies (GWAS) that will identify common genetic factors that influence health and disease. The information derived from such studies will be essential for developing new approaches to reduce disease burden, promote health, and understand individual differences in health. GWAS are currently defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition.

Researchers have known since the first analysis of the draft human genome sequence in 2000 that people are 99.9 percent identical at the genetic level. Within that 0.1 percent, where people differ one from the other, however, lies the reason why one person has a higher risk of a common disease, such as diabetes, than someone else. Studies show that common variations exist across the genome; GWAS will systematically associate the common variations with specific common diseases. Whereas past genetic research found strong effects from single gene defects that caused rare inherited diseases, such as cystic fibrosis or muscular dystrophy, GWAS will identify many genetic variations that, when summed, produce an increased relative risk for common diseases, such as cancer or Alzheimer's disease. The genetic variations identified by GWAS may also identify combinations of genetic variation that confer good health (i.e., lower relative risks) and even show doctors which medications will best work to treat an individual with a given genetic makeup.

In many ways, the results from GWAS will provide the information physicians need to interpret an individual's genome once it has been sequenced by the technologies described in the sequencing technology section above.

Those results will be arriving rapidly over the next few years. The diseases for which results already are available include age-related eye diseases, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), schizophrenia, and psoriasis.

In addition, recent reports have appeared in the scientific literature on a wide range of GWAS findings, including:

1. *Type 2 diabetes:* Three scientific reports in April, including one involving NHGRI, linked 10 genes to Type 2 diabetes.

2. *Coronary heart disease:* Two studies linked genetic markers on chromosome 9 with coronary heart disease and heart attacks. Moreover, one of the genetic variants in the heart studies appeared in the same region as a genetic variant in the Type 2 diabetes studies reported earlier in the month.

3. *Adult obesity:* One study linked one form of a single gene to body mass index and discovered it predisposes to childhood and adult obesity.

4. *Adult height:* Another study linked a gene variation to height in different populations around the world.

5. *AIDS:* The first GWA study of an infectious disease provided new insights into why some patients suffer less harm during an acute infection with human immunodeficiency virus (HIV) than others who are less able to suppress the virus that causes AIDS. The insights may well lead to more effective treatments.

6. *Age-related macular degeneration:* One of the earliest modern GWAS discoveries found a relationship of a gene involved in an inflammatory response with a type of blindness that occurs in elderly individuals. The discovery immediately suggested a therapeutic intervention that should slow the progression of the blindness.

7. Results from numerous other disease-related GWA studies have begun producing results on various disorders, such as glaucoma, Type 1 diabetes, breast cancer, Crohn's disease, prostate cancer, rheumatoid arthritis, multiple sclerosis, and asthma. Results from illnesses being studied with the GWAS strategy have risen dramatically, and equally dramatic results can be expected in the next few years.

Other advances are expected from large-scale projects launched by several of the NIH's Institutes and Centers, including the Framingham Genetic Research Study, launched by the National Heart, Lung, and Blood Institute in February 2007, in which 9,000 participants of the long-running Framingham Heart Study will undergo genomic analysis. The National Cancer Institute (NCI) also launched a GWAS aimed at identifying the genes involved in cancers of the breast and prostate. The 3-year, $14 million initiative was launched in 2006.

Through a series of GWA studies, using samples from existing case-control studies of patients with common diseases, these projects will contribute to the identification of genetic pathways that make us more susceptible to these diseases and thus facilitate discovery of new molecular targets for prevention, diagnosis, and treatment.

Status and Next Steps

- After a period of public consultation, the NIH in August released a new policy for Genome-Wide Association Studies supported and conducted by NIH. The policy addresses (1) data-sharing procedures, (2) data-access principles, (3) intellectual property, and (4) issues regarding the protection of research participants through all phases of GWAS. Many of the principles contained in the policy reflect and extend existing NIH polices and other recent NIH discussions. The GWAS policy will be applicable to competing grant applications, proposals for contracts, and intramural research projects beginning on January 25, 2008. The policy can be accessed at http://www.genome.gov/19518660.

The National Library of Medicine (NLM) recently initiated a new database known as dbGaP to distribute data from GWAS. dbGaP, the database of Genotype and Phenotype, will for the first time provide a central location for interested parties to see all study documentation and to view summaries of the measured variables in an organized and searchable Web format. Already, the NIH database of Genotype and Phenotype (dbGaP) makes data from several GWA studies freely available to researchers around the world. See http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap.

Genes, Environment and Health Initiative

National Institutes of Health
http://www.gei.nih.gov/

Description

On February 8, 2006, Health and Human Services Secretary Michael O. Leavitt announced a plan to implement a Genes, Environment and Health Initiative (GEI). The GEI will have two main components:

- The Genetics Program is a pipeline for analyzing genetic variation in groups of patients with specific illnesses.
- The Exposure Biology Program is an environmental technology development program to produce and validate new methods for monitoring environmental exposures that interact with a genetic variation to result in human diseases. The program importantly also includes developing new methods for identifying individual biological response to environmental exposures.

This initiative includes funding for genome-wide association studies, methods of analyzing gene-environment interactions, environmental "sensors" that detect exposure, and measurement of diet and physical activity.

Status and Next Steps

In September, NIH announced the first round of first-year funding under GEI, committing $40 million in new funding provided for the initiative, in addition to another $9 million provided by two NIH Institutes to support GEI-related studies. In the first year, NIH will fund eight genome-wide association studies, two genotyping centers, a coordinating center, and more than 30 environmental technology projects. Details can be found at http://www.nih.gov/news/pr/sep2007/nhgri-04.htm.

GWA studies will focus on the genetics of addiction, coronary heart disease, lung cancer, Type 2 diabetes, maternal metabolism and birth weight, prematurity, and oral clefts. Environmental studies will include 34 projects on the development of sensors for personal exposure assessment, measurement of psychological stress and addictive substances, diet and physical activity, and biological response indicators of environmental stress.

Human Genome Epidemiology Network

Centers for Disease Control and Prevention
http://www.cdc.gov/genomics/hugenet

Description

The Human Genome Epidemiology Network (HuGENet™) is a voluntary, international collaboration committed to translating genetic research findings into opportunities for preventive medicine and public health. HuGENet™ promotes the integration and synthesis of population-based epidemiologic data describing the interactions of genetic variants with modifiable risk factors and their joint contributions to disease risk. Established by the Centers for Disease Control and Prevention (CDC) in 1998, HuGENet™ now includes coordinating centers in the United Kingdom, Canada, and Greece. The network's free online resources include a weekly summary of new scientific articles on human genome epidemiology, a searchable database, case studies for training, and information on workshops and publications.

Status and Next Steps

- HuGENet™ collaborators recently published "A road map for efficient and reliable human genome epidemiology" in *Nature Genetics* [2006;38(1):3-5], describing a Network of Investigator Networks for sharing best practices, tools, and methods for analysis of associations between genetic variation and common diseases.
- In 2006, HuGENet™ published an online handbook for systematic reviews and meta-analyses (http://www.cdc.gov/genomics/hugenet/reviews/guidelines.htm), which are peer-reviewed and published in partnership with 10 scientific journals. Currently, 58 HuGE Reviews are available online.
- HuGE Pub Lit, the curated, searchable database based on weekly sweeps of PubMed, currently contains more than 26,000 citations indexed by gene, health outcome, and personal or environmental factors.
- Criteria for evaluating the evidence for gene-disease association were drafted at an international meeting in Venice in November 2006 and are awaiting publication.
- CDC will continue to collaborate with national and international partners to provide leadership, guidance, and support for the collection and synthesis of population-based data on genetic variation in health and disease.

National Health and Nutrition Examination Survey

Centers for Disease Control and Prevention
http://www.cdc.gov/nchs/nhanes.htm

Description

The National Health Survey Act of 1956 provided the authority for a continuing survey to provide current statistical data on the amount, distribution, and effects of illness and disability in the United States. National Health and Nutrition Examination Survey (NHANES) was created to fulfill the purpose of this act.

NHANES provides a basis for personalized health care by providing databases, infrastructure, and research capabilities to understand individual differences in risk factors for disease and practical information to guide patient care decision-making.

Status and Next Steps

NHANES data are collected from a representative sample of communities throughout the United States.

The current NHANES is the eighth in a series of national examination studies conducted in the United States since 1960. The goals of NHANES are as follows:

- To estimate the number and percentage of persons in the U.S. population and designated subgroups with selected diseases and risk factors.
- To monitor trends in the prevalence, awareness, treatment, and control of selected diseases.
- To monitor trends in risk behaviors and environmental exposures.
- To analyze risk factors for selected diseases.
- To study the relationship between diet, nutrition, and health.
- To explore emerging public health issues and new technologies.
- To establish a national probability sample of specimens for genetic analyses:
  - CDC has defined a “top 100” list of genetic variants of public health significance, and is currently leading a collaborative effort with the NCI to determine how common these variants are in the U.S. population, using over 7,000 biologic specimens collected in NHANES III. This work will be completed later this year and will provide a foundation for further studies to understand how genetic variation contributes to human disease.

CDC and the CDC Foundation are launching a new initiative, Beyond Gene Discovery (BGD), to measure hundreds of thousands of genetic variants in about 15,000 NHANES biologic specimens, and to coordinate the comprehensive analysis of associations among variations in genotype, phenotype, and gene-environment interaction.

Biomarkers Consortium

http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml

Description

The development of biomarkers is being carried out by work in several NIH Institutes, as well as through the Biomarkers Consortium. The Consortium is a public-private biomedical research partnership of the Foundation for the NIH that involves a variety of public and private stakeholders including the NIH; U.S. Food and Drug Administration (FDA); Centers for Medicare & Medicaid Services (CMS); pharmaceutical, biotechnology, diagnostics, and medical device industries; nonprofit organizations and associations; and advocacy groups. The goals include accelerating disease-specific research and ensuring that safe, innovative, and effective medicines and diagnostics are expeditiously developed to address health care needs, improve medical care, and promote and improve public health. The Biomarkers Consortium facilitates personalized health care by developing tools and information that facilitate understanding about individual differences in disease conditions.

Status and Next Steps

The Consortium's first project will be to qualify a method to use imaging methods to detect tumor response to new chemotherapy agents. A method known as fluorodeoxyglucose positron emission tomography (FDG-PET) is considered a potential biomarker for response of cancer to treatment. FDG-PET measures glucose uptake by tumors using a radioactive form of fluorine incorporated in a sugar molecule. Tissues that accumulate radioactive glucose are visible through positron emission tomography (PET), an imaging method to detect gamma rays.

Researchers believe that FDG-PET could become a tool for gauging a cancer patient's response to chemotherapy or radiation by accurately measuring tumor metabolism. Physicians will thereby rapidly know whether the tumor is responding to therapy or when to switch therapies to provide the best chance for curing or managing the cancer. FDG-PET can also assist clinical research and drug development by helping to assess a study subject's response to investigational drugs.

Initially, the Consortium will focus its FDG-PET efforts on non-Hodgkin's lymphoma and lung cancer. Non-Hodgkin's lymphoma strikes over 55,000 Americans each year and kills close to 20,000 according to the NCI. Lung cancer makes up 13 percent of all cancer cases in the United States. More than 170,000 individuals are diagnosed with lung cancer each year, and close to that number die from the disease. Although it was once thought to almost exclusively be caused by smoking, approximately 13 percent of lung cancer patients have never smoked.

NIH Biomarkers Projects

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The Osteoarthritis Initiative

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) places a high priority on studies to identify risk factors and biomarkers of disease in an effort to facilitate the early identification of signs and symptoms and to develop interventions that are more effective. To this end, the Institute will continue its commitment to a novel public-private partnership to improve prevention of osteoarthritis (OA), or degenerative joint disease. The Osteoarthritis Initiative (OAI) is a long-term effort, developed with support from numerous NIH components and private sector sponsors, and with the participation of the FDA, to create a publicly available research resource to identify and evaluate biomarkers of OA for use in clinical research. The study has 4,800 participants who are at high risk for knee OA, and, as of early FY 2007, clinical data from approximately 2,000 of them were available for research projects. Over the next 5 years,

the OAI will provide an unparalleled, state-of-the-art longitudinal database of images and clinical outcome information to researchers worldwide to facilitate the discovery of biomarkers for development and progression of OA. In this effort, a biomarker would be a physical sign or biological substance that indicates changes in bone or cartilage. Today, 35 million people, 13 percent of the U.S. population, are ages 65 and older, and more than half of them have radiological evidence of OA in at least one joint. By 2030, an estimated 20 percent of Americans, about 70 million people, will have passed their 65th birthday and will be at increased risk for OA.

National Institute of Diabetes and Digestive and Kidney Diseases

Biomarkers Predicting Disease Onset and Progression

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has a long track record of successfully promoting the development of biomarkers for a number of diseases within its research mission that have transformed patient care. However, additional biomarkers are urgently needed to aid in predicting disease as well as monitoring disease progression and response to therapy. The NIDDK is spearheading several efforts to pursue potential biomarkers, such as (1) Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) II, which is following 200 patients (who were part of the original CRISP study) who have autosomal-dominant PKD. The goal is to verify findings of the initial CRISP study and determine whether changes in anatomic characteristics of their kidneys as measured by magnetic resonance imaging are useful in providing surrogate measures for disease progression, (2) Chronic Renal Insufficiency Cohort Study (CRIC) and Chronic Kidney Disease in Children (CKiD), which will be looking for nontraditional biomarkers for cardiovascular disease risk, chronic kidney disease progression, and cognitive changes (in children), (3) Biomarker Development for Diabetic Complications, which encourages research on biomarkers that can help identify patients with diabetes who are at particular risk for various comorbidities, and (4) Development of Disease Biomarkers, which will provide resources to demonstrate that candidate biomarkers meaningfully reflect actual disease processes. The Initiative's scope includes well-defined human diseases of liver, kidney, genitourinary tract, and digestive and hematologic systems; endocrine and metabolic disorders; diabetes and its complications; and obesity. New biomarkers not only may improve ability to predict disease, but also can be used to measure effects of new candidate therapies and aid in the design and conduct of clinical trials.

National Institute of Neurological Disorders and Stroke

Biomarkers for Neurodegeneration

Biomarkers can enhance the treatment of individual patients and expedite clinical trials of new therapies by predicting who is likely to develop a disease and who might benefit from or be harmed by a particular treatment, or by giving early indications of how a disease is progressing or whether a therapy is working. The National Institute of Neurological Disorders and Stroke (NINDS) strategic and disease specific plans have highlighted the importance of biomarkers, and the Institute is supporting increasing numbers of biomarker studies in disorders that include Alzheimer's disease, brain tumors, epilepsy, Huntington's disease, multiple sclerosis, Parkinson's disease, stroke, traumatic brain injury, and cognitive impairment in HIV infection, as well as biomarkers to indicate exposure to chemical nerve agents. The NIH Neuroscience Blueprint, in which NINDS participates, is soliciting additional studies of biomarkers for neurodegeneration in FY 2007. As one example of biomarkers studies, NINDS intramural researchers are conducting the BioMS study in conjunction with a multisite extramural Phase III clinical trial of combination therapies for multiple sclerosis, the CombiRx trial. BioMS is applying genetic mapping, gene expression studies, histocompatibility typing, and proteomics technology to data from up to 1,000 patients in the clinical trial and will relate the findings back to the clinical outcome data and the brain imaging from the CombiRx trial to identify biomarkers.

National Institute on Alcohol Abuse and Alcoholism

Alcoholism-Related Biomarkers

Alcoholism is often a hidden disease. Unlike other abused drugs, the majority of alcohol molecules in the body are rapidly metabolized to carbon dioxide and water. Therefore in the absence of accurate self-report it is difficult to detect when an individual is consuming alcohol in a harmful pattern. A small fraction of alcohol, however, is metabolized to form other compounds that have a longer half-life. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is exploring the utility of such biomarkers so that individuals who are drinking in a harmful manner can be identified and receive the appropriate intervention before their drinking leads to adverse health outcomes. Biomarkers can also be used to identify individuals who have relapsed to harmful drinking. Specifically, there is encouraging research on nonoxidative markers of alcohol including ethyl glucuronide (EtG), ethyl sulfate, and phosphatidyl ethanol that NIAAA will continue to pursue in addition to using state-of-the-art technologies to develop additional biomarkers. Biomarkers will also be a valuable tool in assessing in utero exposure to alcohol in newborn infants. Specifically, fatty acid ethyl esters are being actively tested as markers for exposure to alcohol in the last few months of gestation. An indication of alcohol exposure during pregnancy would be predictive of children who should be assessed for neurological and physical deficits.

Cancer Research Programs Supporting Personalized Health Care

National Cancer Institute, National Institutes of Health

Description

The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov/index.asp) is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The pilot project will assess the feasibility of a full-scale effort to systematically explore the entire spectrum of genomic changes involved in cancer of the brain, lung, and ovary. The Cancer Genome Atlas Pilot Project establishes an integrated network of core resources and specialized genome characterization and genome sequencing centers that will work together to form a system that selects genes and regions in order to drive high-throughput cancer genome sequencing. The project contributes to personalized health care by establishing the mechanisms and individual differences in the genetic causes of these types of cancer. TCGA is jointly supported by NCI and the National Human Genome Research Institute.

The NCI is launching the NCI Community Cancer Centers Program (NCCCP) (http://www.cancer.gov/researchandfunding/ncccp-pilot-program) as a pilot program to bring the latest scientific advances and the highest level of innovative and integrated, multispecialty care to a much larger population of cancer patients. The overarching goal is to bring science, early-phase clinical research, and optimal evidence-based therapies to patients in their home communities. Pilot sites will also share best practices and refine the overall concept as a prelude to launching a new national network of research-driven cancer care at the community level.

Status and Next Steps

- Researchers have found that a unique pattern of activity for genes in cells located in the tissue surrounding a liver tumor can accurately predict whether the cancer will spread to other parts of the liver or to other parts of the body. They have also identified new biomarkers that may be useful in diagnosing early disease.
- A large-scale analysis of data on breast cancer risk has concluded that a common variation in the gene caspase-8 (*CASP8*) is associated with a somewhat lower risk of the disease. Variants are small changes that occur in a gene sequence.

- Scientists have discovered how human T cell leukemia virus type 1 (HTLV-1), which infects about 20 million people worldwide, evades being held in check by one of the body's natural defense mechanisms. (An active infection with HTLV-1 leads to T cell leukemia in up to 5 percent of all cases worldwide.)

These programs are part of an infrastructure that will develop resources to support discovery of new genetic markers of cancer that can be used to identify individuals at risk for them. Completion of these pilot projects will establish a research capability to support individualized approaches to health care.

Office of Biorepositories and Biospecimen Research
National Cancer Institute, National Institutes of Health
http://biospecimens.cancer.gov/

Description

The Office of Biorepositories and Biospecimen Research (OBBR) was established at the NCI in 2005 to facilitate and accelerate the development of personalized cancer medicine by ensuring the availability of high-quality, clinically annotated human specimens for postgenomic cancer research. Toward this end, the OBBR is committed to the development of evidence-based standards of biospecimen acquisition, processing, and storage that optimally preserve the quality and integrity of biospecimens for molecular analysis and ensure reproducibility of molecular tests performed on those specimens. Such standards will become the standards of pathology/laboratory medicine practice in an era of personalized medicine.

Status and Next Steps

- In order to create a baseline to assess, improve, and ensure the quality of human biospecimen resources, the OBBR has developed a comprehensive set of state-of-the-science guidelines for biobanking, *NCI Best Practices for Biospecimen Resources.* The *Best Practices*, accepted in final form by the National Cancer Advisory Board in June 2007, will serve as the national standard, while OBBR engages in a stepwise process of increasing the scientific base for further data-driven standards and operating procedures that are molecular analysis platform-appropriate.

- The *Best Practices* guidelines also have served as the basis for a comprehensive set of *Biospecimen Resource Evaluation Criteria* (the BRET) developed by the OBBR that can be used to objectively assess the quality of any existing or planned biospecimen resources based on the current state of the science.

- The OBBR has developed an intramural Biospecimen Research Network (BRN) and an extramural program known as Biospecimen Research for Molecular Medicine to systematically investigate the effects of acquisition, processing, and storage variables on biomolecular profiles in specimens. Such data will form the scientific basis of data-driven procedures for patient specimen handling in molecular medicine.

- The OBBR has established collaborations on data-driven protocol development with authoritative professional organizations like the College of American Pathologists that can both monitor implementation through its Laboratory Accreditation Program and educate its constituents about the importance and practicalities of compliance with these new standards.

- The *Best Practices* guidelines advocate cost recovery but not profit-generating business models for biospecimen resources. In order to help biospecimen resources define actual costs in a modular fashion that can be customized to any given resource model, OBBR has undertaken a Biobanking Economics initiative and plans to publish guidance for cost recovery on the basis of the findings.

- The OBBR is collaborating in transformative, large-scale NCI strategic initiatives that will enable personalized medicine in which the principles of high-quality shared biospecimen resources are

critical for achieving the research goals. Such projects include those that emphasize high-quality biospecimens as shared resources for cancer researchers, such as the NCI Community Cancer Centers Program; caBIG™ projects; The Cancer Genome Atlas; Clinical Proteomic Technologies Assessment for Cancer; and the Nanotechnology Alliance.

- The OBBR also has established collaborations with other major initiatives outside the NCI, nationally and internationally, to achieve global harmonization of approaches to biospecimen issues throughout the translational research enterprise. Projects include the Interagency (NCI, FDA, CMS) Oncology Task Force and the Biomarkers Collaborative (NCI, FDA, AACR).

- The OBBR is committed to the development of educational tools and resources for all potential stakeholders (public, professional, private) that address the spectrum of issues related to human biospecimens in order to align interested constituencies on the importance of high-quality shared biospecimen resources. Projects include OBBR Web site enhancements for biospecimen research and resource data sharing; development of educational programs for professionals; outreach to patient advocacy groups; and development of hands-on training programs for biobankers.

National Program of Cancer Registries
Centers for Disease Control and Prevention
http://www.cdc.gov/cancer/npcr/

Description

State-based cancer registries are data systems that collect, manage, and analyze data about cancer cases and cancer deaths. In each State, medical facilities (including hospitals, physicians' offices, therapeutic radiation facilities, freestanding surgical centers, and pathology laboratories) report these data to a central cancer registry. Established by Congress through the Cancer Registries Amendment Act in 1992, and administered by the CDC, the National Program of Cancer Registries (NPCR) collects data on the occurrence of cancer; type, extent, and location of the cancer; and type of initial treatment.

Status and Next Steps

- Before NPCR was established, 10 States had no registry, and most States with registries lacked the resources and legislative support they needed to gather complete data. Today, NPCR supports central cancer registries in 45 States, the District of Columbia, Puerto Rico, the Republic of Palau, and the Virgin Islands. These data represent 96 percent of the U.S. population. Together, NPCR and the NCI's Surveillance, Epidemiology, and End Results (SEER) Program collect data for the entire U.S. population.

- Since 2002, CDC and NCI have combined their data sources to publish annual Federal cancer statistics in the *United States Cancer Statistics (USCS): Incidence and Mortality* report, produced in collaboration with the North American Association of Central Cancer Registries. This year's report includes cancer incidence data from registries covering 96 percent of the U.S. population, and mortality data from all States and the District of Columbia.

- CDC has collaborated with NPCR-funded programs to define, test, and release NPCR data in WONDER, an online reporting system hosted at CDC. This new system, launched in early 2006, allows more access to NPCR data than previously was available. Finding critical data that can help guide and evaluate interventions focused on cancer prevention and control now is easier than ever.

- NPCR has developed software programs to make the process of submitting data easier for hospitals. By standardizing the way data are checked for validity, EDITS software improves data quality. Hospitals also can use any of the Registry Plus suite of programs for routine or special data collection. CDC provides and distributes these software programs, which are compliant with national standards, free of charge to the public health community.

Heart, Lung, and Blood Research Programs Supporting PHC

National Heart, Lung, and Blood Institute, National Institutes of Health
http://www.nhlbi.nih.gov/

Description

The National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the Boston University School of Medicine, have launched a comprehensive new effort to enable identification of genes underlying cardiovascular and other chronic diseases. The new effort, the Framingham SNP Health Association Resource (SHARe), builds upon the long-running Framingham Heart Study (FHS) and will involve up to 500,000 genetic analyses of the DNA of 9,000 study participants across three generations.

Previous NIH-funded research charted the pattern of genetic variation in the human genome and demonstrated that common but minute variations, called single nucleotide polymorphisms (SNPs), in human DNA can be used to identify genetic contributions to common diseases. The Framingham SHARe will provide an incomparable resource for investigators that will enable them to combine the wealth of data collected over the years in the FHS on disease and disease risk factors with the new genetic data to identify genetic variants that predispose individuals to cardiovascular and other major chronic diseases.

Status and Next Steps

- This year, the Framingham Heart Study will be reporting results on a Genome-Wide Association Study. DNA from each of approximately 8,000 participants across all three generations will be studied for about 500,000 unique genetic changes. Using computer programs, researchers will relate this large catalogue of genetic results to many of the clinical and laboratory measurements that have been made in study participants during their examinations. Researchers hope to be able to identify genetic variations that are most strongly related to study participant characteristics such as levels of cholesterol, systolic blood pressure, obesity, and diabetes, and to disease occurrences such as heart attack, stroke, and osteoporosis.
- Research recently evaluated multiple biomarkers for the prediction of first major cardiovascular events and death. The newer biomarkers such as natriuretic peptides, C-reactive protein, fibrinogen, urinary albumin, and homocysteine were compared with established risk factors such as high blood pressure, diabetes, and high cholesterol. Measuring several biomarkers simultaneously, referred to as the “multimarker” approach, has enabled the scientists to stratify risk. They found that persons with high multimarker scores had a risk of death four times as great and a risk of major cardiovascular events almost two times as great as persons with low multimarker scores.

Eye Research Programs Supporting PHC

National Eye Institute, National Institutes of Health
http://www.nei.nih.gov/

Description

Over the past 15 years, nearly 500 genes that contribute to inherited eye diseases have been identified. Disease-causing mutations are associated with many ocular diseases, including glaucoma, cataracts, strabismus, corneal dystrophies and a number of forms of retinal degenerations. This remarkable new genetic information highlights the significant inroads that are being made in understanding the medical basis of human ophthalmic diseases. As a result, gene-based therapies are actively being pursued to ameliorate ophthalmic genetic diseases that were once considered untreatable. This project will support better understanding of new ways to personalize prevention and treatment of vision loss. The National Ophthalmic Disease Genotyping Network (eyeGENE™) is at http://www.nei.nih.gov/resources/eyegene.asp.

Status and Next Steps

- The first organizational meeting of the eyeGENE™ was convened January 10-11, 2006, to discuss the milestones necessary to launch the eyeGENE™ initiative. Participants included members of the ophthalmic, optometric, and genetic communities. Experts in bioethics and Federal regulatory requirements were also present as were members of the international vision research community.

- A team of researchers has determined that variations in certain genes involved in fighting infection can successfully predict the risk of developing age-related macular degeneration (AMD), the leading cause of blindness in white Americans older than age 60. Researchers identified a genetic variant that is associated with an increased risk of developing AMD. Future goals include:

  - Discovery of genetic causes of eye diseases
  - A pathway for determining accurate diagnostic genotyping to patients with inherited eye diseases
  - Improved public and professional awareness of genotype/phenotype resources for persons with inherited diseases that affect the visual system, their clinicians, and scientists studying these diseases
  - Large datasets necessary to identify novel genetic risk factors for ocular diseases
  - Refinement/standardization of clinical descriptive terminology for complex ocular diseases
  - A shared database of genotype/phenotype information

II. Health Information Technology

American Health Information Community

http://www.hhs.gov/healthit/

Description

The American Health Information Community (AHIC) was chartered in 2005 to make recommendations to the Secretary of HHS on how to accelerate the development and adoption of health information technology. AHIC was formed to help advance efforts to reach President Bush's goal for most Americans to have electronic health records within 10 years. It provides input and recommendations to HHS on how to make health records digital and interoperable and ensure that the privacy and security of those records are protected, in a smooth, market-led way.

Status and Next Steps

In May 2006, the AHIC delivered its first set of recommendations to the Secretary of HHS. The Secretary officially accepted these recommendations, which were in four areas of focus:

- *Consumer Empowerment.* To create a consumer-directed and secure electronic health-care registration information and medication history for patients.
- *Chronic Care.* To use secure messaging, such as e-mail, for communication between patients and their health-care providers.
- *Electronic Health Records.* To create standardized, secure records of past and current laboratory test results that are accessible by health professionals.
- *Biosurveillance.* To enable the transfer of standardized and de-identified health data to authorized public health agencies within 24 hours.

In addition, AHIC has made significant progress in standards harmonization:

- The AHIC recommended three sets of "Interoperability Specifications" approved by the Health Information Technology Standards Panel (HITSP), a standards panel established by the American National Standards Institute (ANSI) to help in harmonizing hundreds of competing standards. Secretary Leavitt accepted these standards, which form the basis of interoperability.

In 2006, AHIC created three new workgroups to make recommendations to the AHIC, which in turn will provide recommendations to the Secretary:

- Confidentiality, Privacy, and Security
- Health Care Quality
- Personalized Health Care

Information on the PHC Workgroup is at http://www.hhs.gov/healthit/ahic/healthcare/.

Office of the National Coordinator for Health Information Technology

Office of the Secretary of HHS
http://www.hhs.gov/healthit/onc/mission/

Description

The Office of the National Coordinator for Health Information Technology (ONC) provides counsel to the Secretary of HHS and Departmental leadership for the development and nationwide implementation of an interoperable health information technology infrastructure. The ONC also provides management of and logistical support for the AHIC. The National Coordinator for Health Information Technology serves as the Secretary's principal advisor on the development, application, and use of health information technology.

Status and Next Steps

Accomplishments leading up to 2007 have laid the foundation of a robust health information technology (IT) initiative that is already bringing value to health care consumers and providers. With the organizations and contracts in place and a standards process established, additional progress in the year ahead will be rapid.

- *Product Certification.* The Certification Commission for Healthcare Information Technology (CCHIT) certified more than 80 ambulatory—or clinician office-based—electronic health record products. The CCHIT seal of approval is awarded to products that meet baseline criteria for functionality, security, and interoperability. This certification encourages adoption IT by assuring providers that their systems can be a part of the future of health IT. See http://www.cchit.org.
- *Changes to Regulations.* HHS issued new regulations to allow certain arrangements in which a hospital or other health care entity donates health IT and training services to physicians and other health care providers. These new regulations will accelerate adoption by giving physicians and other health care providers increased access to EHR software and assistance in implementing health IT. See http://www.hhs.gov/healthit/certification/stark/.
- *Health IT Adoption Measurement.* Through a contract with George Washington University, a health IT adoption survey of physician offices was conducted to establish the baseline for current physician use of electronic health records at 10 percent. The survey also identified the criteria necessary to measure success in encouraging further adoption.
- *Nationwide Health Information Network.* Four prototype architectures for a Nationwide Health Information Network (NHIN) were delivered in January 2007. These prototypes were developed with functional requirements and security and business models for health information exchange. Their delivery marks the beginning of the next phase of NHIN work – to connect the prototypes and State and regional health information exchange efforts in "trial implementations" that will make up the NHIN. See http://www.hhs.gov/healthit/healthnetwork/background/.
- *Privacy and Security Across State Lines.* To ensure that all patients' privacy is consistently protected regardless of where they receive care, a regular forum will convene State leaders to reach consensus on cross-border issues of privacy, security, physician licensure, and health care practice, and the States' roles in health information exchange. In addition, a nationwide summary of State privacy and security assessments, solutions, and implementation plans was recently published. See http://www.healthit.ahrq.gov/privacyandsecurity.
- *The Federal Health Care Delivery System.* Plans will be completed across the Federal Government to implement the requirements of the President's 2006 Executive Order on Value-Driven Health Care in a consistent and effective manner. These plans will apply to the Federal Government's adoption of interoperable health IT within its own delivery system and the contracts it negotiates. See http://www.hhs.gov/valuedriven.

Health Information Technology Initiative

Agency for Healthcare Research and Quality
http://healthit.ahrq.gov

Description

The Agency for Healthcare Research and Quality (AHRQ) initiative on health information technology is a key element of the Nation's 10-year strategy to bring health care into the 21st century by advancing the use of information technology. The AHRQ initiative includes more than $166 million in grants and contracts in 41 States to support and stimulate investment in health IT, especially in rural and underserved areas. Through these and other projects, AHRQ and its partners will identify challenges to health IT adoption and use, solutions and best practices for making health IT work, and tools that will help hospitals and clinicians successfully incorporate new IT.

Status and Next Steps

In 2004, AHRQ established the AHRQ National Resource Center for Health Information Technology to advance the goals of modernizing health care through the best and most effective use of IT. In addition to providing technical assistance, the National Resource Center shares new knowledge and findings that have the potential to transform everyday clinical practice. AHRQ's National Resource Center is committed to advancing our national goal of modernizing health care through the best and most effective use of IT. AHRQ has invested more than $166 million in grants and contracts in 41 States to support and stimulate investment in health IT, especially in rural and underserved areas.

AHRQ has awarded contracts to six States—Colorado, Delaware, Indiana, Rhode Island, Tennessee, and Utah—totaling $34.70 million to help them lead the way in regional health information exchange and collaboration. These States are expanding networks for communication and information-sharing among health care providers, laboratories, major purchasers of health care, public and private payers, hospitals, ambulatory care facilities, home health care providers, and long-term care providers.

Most of AHRQ's health IT grants are 3-year projects, and the five contracts for statewide systems are 5-year projects. These grants and contracts were awarded in the fall of 2004. However, AHRQ will not wait to begin collecting and releasing observations from these projects. Information and interim findings garnered from the projects, as well as from other AHRQ activities, will be shared as quickly as possible through the National Resource Center.

Health Information Technology for Safety Net Providers

Health Resources and Services Administration
http://www.hrsa.gov/healthit/

Description

The Health Resources and Services Administration (HRSA) provides grants and technical assistance for safety net providers to promote the adoption and effective use of health information technology, including electronic medical records and telehealth. HRSA is also working with ONC, CMS, AHRQ, NIH, and CDC to ensure that safety net providers are considered in all HIT adoption efforts.

Status and Next Steps

In support of the President's Health Center Initiative and his goal of universal adoption of electronic health records (EHR) by 2014, HRSA will award up to 8 grants totaling $9.7 million to promote EHR implementation through either a "Health Center Controlled Network" that links several health centers or a large single health center with 30 or more sites. Funds must be used to implement EHRs in at least 15 sites.

The grants support the use of EHRs as a tool to improve the safety, quality, efficiency, and effectiveness of health care delivery. They also will test the ability of health centers and other safety-net providers to adopt and effectively use EHRs, create sustainable business models for deploying HIT, and leverage initiatives and resources to improve quality and health outcomes.

HRSA also is working to expand the number of users of a HRSA Web portal called the HRSA Health Information Technology Community. The site provides a "virtual" meeting place for users, most of whom are staff from health centers, health center networks, and primary care associations. Users take part in online discussions, share documents, and exchange tools and resources on using electronic technology to promote patient safety and quality of care. HRSA will expand access to the site to organizations that receive grants from HRSA's HIV/AIDS Bureau, Maternal and Child Health Bureau, Office of Rural Health Policy, and Office for the Advancement of Telehealth.

Use of Medicare Data To Support Research on Health Outcomes

Centers for Medicare & Medicaid Services
http://www.cms.hhs.gov/

Description

Medicare is the largest health insurance program in the country, and it possesses data on claims, treatments, and outcomes that can be of great value in measuring and improving quality and safety of care. The large volume of Medicare data can help define the effectiveness of treatments for increasingly narrow subgroups of the population – especially the effects of drugs among older Americans. Several opportunities are being pursued for sharing Medicare data in a manner that protects individual privacy while yielding valuable information about treatment effectiveness and value.

Status and Next Steps

Coverage with Evidence Development. For treatments and products where clinical information is limited but promising, Medicare has already instituted a process for providing coverage that is contingent on the collection of new evidence to document effectiveness, called Coverage with Evidence Development (CED). The CMS issued a final guidance document on July 12, 2006, describing the CED concept. This CED guidance describes two processes: coverage with appropriateness determination (CAD) and coverage with study participation (CSP).

- CMS is using registries to provide data for the two national coverage determinations (NCDs) that require CAD: ACC-NCDR registry for implantable cardiac defibrillators and the National Oncologic PET Registry for FDG-PET for cancer.
- There are four NCDs that require CSP: cochlear implantation, PET (FDG) for Alzheimer's disease, anticancer chemotherapy for colorectal cancer, and home use of oxygen. Two of these have trials running: 9 NCI-sponsored clinical trials of anticancer chemotherapy for colorectal cancer and other cancers and an NIH-approved trial evaluating the value of FDG-PET imaging in patients with dementia.

Part D Data. Medicare is also proposing to make available information about drug claims that is available as a result of the Part D drug benefit. On October 18, 2006, the CMS posted a Notice of Proposed Rulemaking that would allow HHS and CMS to use Part D claims data to evaluate Medicare's prescription drug program. Under the proposed rule, other Federal agencies and external researchers would also be able to use the prescription drug data under the same safeguards that exist for Medicare's other data. This would allow the use of Part D claims information that is being collected for payment purposes for other research, analysis, reporting, and other public health functions.

- Research questions that have been previously addressed through analysis of Part A (hospital insurance) and Part B (medical insurance) claims have contributed to very significant improvements in public health, have been critical in assessing the quality of care and costs of care for patients in the Medicare program, and have in many cases spurred other types of research. The final regulation allowing the use of Part D claims data is expected to be published later in 2007.

Best Practices and Quality Measurement. In addition, Medicare is examining ways to share information with national and regional quality collaboratives to help in developing standards of care and "best practices," as well as measuring performance by providers.

III. Intervention Development and Review

Critical Path Initiative To Improve Medical Product Development

U.S. Food and Drug Administration
http://www.fda.gov/oc/initiatives/criticalpath/

Description

The Critical Path Initiative is the FDA effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product.

Status and Next Steps

In keeping with its mission, FDA issued a report, *Challenges and Opportunities on the Critical Path to New Medical Products* in 2004 to address the growing crisis in moving basic discoveries to the market, where they can be made available to patients. The report evaluates how the crisis came about and offers a way forward. It highlights examples of Agency efforts that have improved the critical path and discusses opportunities for future efforts. Finally, the report calls for a joint effort of industry, academia, and the FDA to identify key problems and develop targeted solutions.

In March 2006, FDA published the second of two reports on the Critical Path to medical product development, *Critical Path Opportunities Report and List*. The *Opportunities Report and List* presented 76 specific scientific opportunities that, if undertaken, would help modernize the Critical Path sciences. The opportunities were identified through extensive outreach with patient groups, the pharmaceutical industry, academia, other Federal agencies, and other health-related organizations. More than 30 projects were launched in 2006: http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html.

In May 2007, FDA issued a report on Critical Path Opportunities for Generic Drugs: http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html.

Below are listed some key Critical Path collaborations and research activities currently under way with FDA participation. The activities are organized according to the priority topics discussed in the *Opportunities Report and List*, also available on the Critical Path Web page http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html. Priority topics include the following:

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into the 21st Century

- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations – Pediatrics

Regulatory Submission of Genomic Data in Medical Product Development

U.S. Food and Drug Administration
http://www.fda.gov/cder/genomics/default.htm

Description

The FDA published Guidance for Industry in 2005 entitled Pharmacogenomic Data Submissions. In this guidance, the concept of a voluntary genomic data submission (VGDS) was described along with the FDA's view of the benefits of submitting exploratory genomic data to FDA. In addition the format, process, and review of VGDS were delineated in detail. In 2004, the FDA Interdisciplinary Pharmacogenomic Review Group (IPRG) was organized as a multicenter, multidisciplinary body to review VGDS.

VGDS Process. Over 40 VGDSs throughout the past 3 years have focused on exploratory genomic biomarkers, their use in preclinical and clinical drug development, diagnostic test validation, clinical enrichment study design, assay validation, and data analysis. Submissions have come from a variety of companies including large PhRMA companies, small drug development specialty companies, platform manufacturers, and diagnostic companies. Therapeutic areas covered by VGDS include alcoholism, Alzheimer's disease, anti-infective therapies, asthma, depression, diabetes, hypertension, obesity, oncology, and rheumatoid arthritis. VGDSs have also had a major impact on discussions about clinical trial design. Major questions submitted within several VGDSs have focused on the design of clinical trials to qualify exploratory biomarkers in a co-development context. VGDSs have also encouraged submissions of genomic data as a part of INDs, NDAs, and BLAs. Consults for genomic data in regulatory submissions have increased on a par with VGDS meetings.

VGDSs have been submitted to FDA. VGDSs have served to facilitate bilateral exchange and training of regulatory scientists on the technology and application of genomic biomarkers. They have also familiarized industry with the review capabilities within the regulatory authorities and allowed regulators to share their thinking about genomics. Experience gained through VGDS has led to the development of a Pilot Process for Qualification of Biomarkers for use in regulatory decisions.

Over the past 3 years, genomic biomarkers have been supplemented by proteomic, metabolomic, imaging, and fluorescence-activated cell sorting assays. For this reason, the VGDS program has been called the Voluntary Biomarker Data Submission program, or VXDS where X indicates a biomarker from one of many scientific domains.

VGDS guidance can be seen at http://www.fda.gov/cber/gdlns/pharmdtasubcomp.pdf, and FDA-EMEA VGDS guiding principles can be seen at http://www.fda.gov/cder/genomics/FDAEMEA.pdf.

Status and Next Steps

VXDS and Education. The newer VXDS process has also become a source of information for the development of educational offerings in personalized medicine. Gaps in the integration of genomic diagnostic tests into medical practice can be bridged with the learning through multidisciplinary educational programs for physicians, nurses, pharmacists, laboratory personnel, and others associated with personalized medicine. Didactic and Web-based courses are being developed by the FDA.

Companion Guidance for the Pharmacogenomic Guidance. A Companion Guidance for the Pharmacogenomics Guidance has been drafted to recommend protocols in the generation of genomic data from microarrays where a consensus exists for their use and to encourage a discussion leading to a consensus where it is currently lacking. This Companion Guidance has its roots in VXDSs and the experience the FDA has gained from these VXDSs regarding the need for a consensus on how genomic data are generated, reported, and reviewed.

Microarray Quality Control Consortium. This experience has also led to the development of collaborative consortia such as the Microarray Quality Control Consortium (MAQC) to identify sources of variability in the generation of genomic data from microarrays. In its initial phase, MAQC identified sources of variability in the generation of differential gene expression data. MAQC is currently in a second phase, focused on the identification of sources of variability in the determination of predictive genomic signatures.

Predictive Safety Testing Consortium. A collaborative consortium has also been developed to help bridge the gap between exploratory and qualified biomarkers. The Predictive Safety Testing Consortium (PSTC) is working through the C-Path Institute to share data, biomarkers, and nonclinical and clinical samples for the qualifications of nonclinical and clinical biomarkers of safety. The PSTC is a key tool in taking drug-independent exploratory biomarkers into qualification through the Pilot Process for Qualification of Biomarkers.

Review of Genetic Tests for Use in Clinical Practice

U.S. Food and Drug Administration
www.fda.gov/cdrh/oivd

Description

FDA regulates commercially distributed test kits and systems in a comprehensive and transparent manner and ensures quality of these tests through premarket review, application of requirements for good manufacturing practices, and application of a system for postmarket patient safety surveillance. While FDA regulation is not the only path to market for genetic tests and other biomarkers for use in personalized medicine, it provides unique assurances of product quality and safety through a program of independent validation of test performance and labeling.

To date FDA has cleared about a dozen cutting-edge new diagnostics for use in promoting personalized medicine including such tests as the Roche AmpliChip CYP450 test, the Third Wave test for UGT1A1, three tests for cystic fibrosis, the Veridex Circulating Tumor Cell Assay, and the first U.S.-cleared expression array – the Agendia MammaPrint. There are dozens more novel diagnostic devices in the developmental pipeline. Cleared and approved product reviews are prominently published on the Office of In Vitro Diagnostic Devices Web page (see Web page above) in two databases: the 510(k) database for some Class I and most Class II products and the PMA database for most Class III products. Summaries of FDA reviews are a matter of public record and can be used by informed laboratorians, health care consumers and advocates, and companies to determine the types of information evaluated by FDA in its premarket review process. Posting of this information allows transparency in regulation and communication of the scientific underpinning of diagnostic devices (old and new) on a product-specific basis.

FDA has been proactive in developing guidances to provide clear roadmaps to facilitate the transition of new products from the research bench to the medical bedside. FDA also has a regulatory toolbox in place that provides for up-front industry-FDA interaction with protocol reviews, expedited reviews for products of public health import, real-time reviews to ensure efficient interactive and rapid review times, and flexible down-classifications under the de novo review process for products with features that ensure low risk in use.

FDA review of diagnostic devices has been advanced by recent statutory changes including the charge by Congress to ensure "least burdensome" regulatory reviews and to provide additional scientific resources and training by implementation of device user fee programs.

FDA has also been proactive in educating stakeholders in its regulatory and scientific work processes. The agency routinely participates in more then two dozen outreach talks per year in the areas of biomarker development, genomics, and personalized medicine; has cosponsored a joint workshop with AdvaMed in 2006 to address issues of importance in pharmacogenomics; and holds a yearly joint training program with industry designed for novice regulatory affairs personnel on how to submit good premarket submissions.

Status and Next Steps

Over the past 5 years, FDA has published almost a dozen guidance documents relevant to development of tests to support personalized medicine. These include:

Class II Special Controls Guidance Document: Factor V Leiden DNA Mutation Detection Systems – Guidance for Industry and FDA Staff – March 2004. This document was the first FDA-published guidance for clearance of a widely used genetic test system for predisposition to clotting disorders. It represented a milestone in pragmatic approaches to establishing analytical performance, classification flexibility, and use of existing clinical literature to support clinical use. http://www.fda.gov/cdrh/oivd/guidance/1236.html

Instrumentation for Clinical Multiplex Test Systems – Class II Special Controls Guidance Document – Guidance for Industry and FDA Staff – March 2005. This document provides general advice on FDA premarket review criteria for multiplex signal measurement instrument systems. It was published with FDA guidance on drug metabolizing enzyme genotyping (http://www.fda.gov/cdrh/oivd/guidance/1551.pdf) to allow clearance of the first microarray system for genetic determinations for metabolic enzyme activity. It provides information on basic hardware, software, and analytical study requirements for this type of system. http://www.fda.gov/cdrh/oivd/guidance/1546.html

Drug-Diagnostic Co-Development Concept Paper – April 2005. This concept paper provides a preliminary but comprehensive overview of administrative and scientific issues of importance in the co-development of a drug in parallel with use of a diagnostic product. http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

Class II Special Controls Guidance Document: RNA Preanalytical Systems (RNA Collection, Stabilization and Purification Systems for RT-PCR used in Molecular Diagnostic Testing) – September 2005. This document provides general advice on how to demonstrate quality and standardized performance for preanalytical accessories to genetic test systems. Given the critical importance of proper collection and processing of genetic samples to ensure quality results, this document provides valuable information for manufacturers to ensure the ability of their test systems to generate reliable results. http://www.fda.gov/cdrh/oivd/guidance/1563.html

CFTR Gene Mutation Detection Systems – Guidance for Industry and FDA Staff – Class II Special Controls Guidance Documents – October 2005. This guidance provides information on approval of the first multiplex system for cystic fibrosis. It utilizes existing literature and practice standards to allow for premarket review without new or additional clinical studies. http://www.fda.gov/cdrh/oivd/guidance/1564.html

Guidance for Industry and FDA Staff – Pharmacogenetic Tests and Genetic Tests for Heritable Markers – June 2007. This document was first issued as a draft in 2003 and then reissued in 2006. It includes concise recommendations on how to establish analytical and clinical performance for new tests. It also provides information on how sponsors can use published literature, when available, to reduce the burden of bringing new tests onto the market by building on existing data and information. http://www.fda.gov/cdrh/oivd/guidance/1549.html

Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable – Guidance for Sponsors, Institutional Review Boards, Clinical Investigators, and FDA Staff – April 2006. This document provides clarification on how researchers and companies developing new tests can have access to leftover samples, while ensuring patient privacy, for product development when samples would otherwise be discarded. http://www.fda.gov/cdrh/oivd/guidance/1588.html

Draft Guidance for Industry, Clinical Laboratories, and FDA Staff – In Vitro Diagnostic Multivariate Index Assays – September 2006 and July 2007. This draft guidance indicates FDA interest in applying its regulatory processes to a small niche of unique diagnostics that integrate multiple signals into a composite signal or score for use in cutting-edge diagnostics. A key criterion for this test category is inability of the health care provider to independently verify or interpret the test result without the help of the test developer. The draft guidance indicates that for tests of this type, whether developed for sale to multiple laboratories or for use at a single laboratory, FDA intends to enforce regulatory requirements. The intent is to ensure that nontransparent tests that are difficult to validate are subject to adequate oversight before being offered in the medical marketplace. http://www.fda.gov/cdrh/oivd/guidance/1610.html

Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Quality Control Material for Cystic Fibrosis Nucleic Acid Assays – January 2007. This document was the first FDA guidance on addressing issues unique to the quality control of genetic tests. Although written specifically for a submission for quality control for cystic fibrosis, principles in this document apply broadly to quality control for other genetic-based methodologies. http://www.fda.gov/cdrh/oivd/guidance/1614.html

Guidance for Industry and FDA Staff – Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests – March 2007. This comprehensive document was developed to assist manufacturers in statistical options for study of diagnostic devices and how to label the devices truthfully and accurately based on the types of studies done to support product intended use(s). http://www.fda.gov/cdrh/osb/guidance/1620.html

Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis – May 2007. This document provides information on FDA premarket review requirements for RNA expression arrays. For the first FDA-cleared test of this type, FDA reviewed studies of the entire molecular signature as a surrogate for individual analytical studies of each biomarker signal and was able to use the information in this control to clear and classify this device in a 60-day total review time. http://www.fda.gov/cdrh/oivd/guidance/1627.html

FDA is also developing additional guidance to assist companies in meeting patient safety requirements including guidance on medical device reporting and recalls, guidance on new molecular diagnostic devices, and guidance on tumor biomarkers. FDA is collaborating actively with multiple NIH partners including the Program on Assessment of Clinical Cancer Tests (PACCT), Early Response Detection Network (EDRN), Specialized Program of Research Excellence (SPORE), and NIH Proteomics Program to develop educational programs, white papers, and research collaborations to advance the development of biomarkers for use in promoting personalized medicine. In some cases, formal MOUs have been developed; in others, work is done on a more informal basis.

FDA is also working with NCI and the American Association for Cancer Research to draft guidelines and recommendations to be used by FDA to create future guidance in areas relevant to advances in regulation of devices and drugs used in personalized medicine. This program includes brainstorming and interaction with multiple stakeholders from academia (both clinicians and laboratorians) and from industry (both drug companies and diagnostic companies). It is hoped that this collaborative work will be the beginning of a successful use of leveraging of multidisciplinary talent to advance FDA's mission of promoting and protecting public health in this important and growing new era of personalized medicine.

Pharmacogenetics Research Network

http://www.nigms.nih.gov/Initiatives/PGRN/

Description

An emerging area of science known as "pharmacogenomics" is yielding new approaches to evaluate individual patients' genomic makeup to determine the best therapy or to guide selection to improve clinical outcome. The NIH Pharmacogenetics Research Network (PGRN) was formed in 2000 to enable a network of multidisciplinary research groups to conduct studies addressing research questions in how genes play a role in differences in individuals' response to therapies, and to populate a knowledge base. Researchers studying this evolving field have formed a network to accelerate progress in this area. These projects are helping develop genetic tests that are now being used in identifying diseases earlier and selecting the right medications for the right patients. These types of studies are helping us understand disparities in the outcomes in certain populations of patients and will help overcome them. Medical research projects are under way to support the connections between the genetic basis of disease and their clinical manifestation.

Status and Next Steps

Described here are examples of research accomplishments:

- *Accurate Dosing of Chemotherapy for Children With Leukemia.* Researchers have made several discoveries that are likely to improve the treatment of childhood leukemia. They looked across the entire genome to discover 124 genes that can explain why some leukemias are resistant to chemotherapy drugs. They also found that differences in two genes can lead to a higher risk for leukemia relapse. Children with these high-risk genes may benefit from more aggressive therapy. On the flip side, the researchers discovered two other gene variations that predispose to a serious side effect when the children are treated with steroids, one of the standard therapies for leukemia.

- *Cancer Drug Label Now Includes Pharmacogenetics Warning.* One finding by researchers spurred changes in the prescription label for irinotecan, a drug approved in 1996 that treats colorectal, lung, and other cancers. Approximately 10 percent of the North American population has two copies of a genetic variation that puts them at higher risk for serious, even life-threatening reactions to irinotecan. In the summer of 2005, the label of the drug was changed to include information about the gene and potential impact and to encourage doctors to use a lower starting dose for patients known to have this variation.

- *Gene Tests Could Indicate Best Asthma Treatment.* Researchers have learned details about how variations in certain sets of genes affect the way people respond to asthma medicines, specifically inhaled steroids and beta agonists. Testing for these genes will help doctors recommend the best treatment for individual patients. Scientists expect to develop prototype tests for the gene variants within a year.

- *Genes Shed Light on Sudden Death From Irregular Heartbeats.* Scientists have tracked down gene variants that put people at higher risk for fatal heart arrhythmias. This information will help doctors target high-risk patients for more aggressive screening and preventive medications. Because some arrhythmias are brought on by medications that treat conditions as diverse as bacterial infection and psychiatric disease, the research will also help doctors tailor medications to individual patients. In the future, it may even lead to new drugs based on gene targets.

- *Pharmacogenetics and Pharmacogenomics Knowledge Base.* A key component of the PGRN is the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a shared online resource that contains pharmacogenetics data from the PGRN and others and is freely available to the entire scientific community. PharmGKB integrates carefully curated and annotated information

about genes, drugs, and diseases, including data about more than 10,000 unique human gene variations involved in drug responses. In addition to facilitating data-sharing, PharmGKB helps researchers identify and fill in knowledge gaps. To protect the privacy of research study participants, names and other identifying information are not stored in this library.

Many grants have been made to researchers to expand the PGRN. Examples of progress in research for the next several years include the study of the genetic basis for variation in response to medications for tobacco dependence or how genetic differences between individuals impact the response to statins, a widely used class of cholesterol-lowering drugs. Results from these and the many other studies funded through the PGRN will enrich the scientific base and inform clinical decision-making.

IV. Integration Into Clinical Practice

Health Data Standards and Genetic Information Resources

National Library of Medicine, National Institutes of Health
http://www.nlm.nih.gov

Description

For more than four decades, the National Library of Medicine (NLM) has conducted and supported groundbreaking research and development related to the representation, interpretation, and use of biomedical knowledge in electronic forms. NLM grants funded much of the important research on artificial intelligence in medicine, clinical reminder and alert systems, decision rules, medical logic modules, and biomedical ontologies. NLM's intramural research and service divisions have made leading contributions to defining useful structures for controlled vocabularies, e.g., MeSH® (Medical Subject Headings); Unified Medical Language System (UMLS®) Metathesaurus®, RxNorm; medical publications, clinical trials descriptions, electronic knowledge bases, e.g., Hepatitis Knowledge Base, Hazardous Substances DataBank, Genetic Home Reference, MedlinePlus; high-resolution anatomic imaging data (the Visible Humans); semantic networks; and effective semantic links between disparate information sources, e.g., TOXNET, Entrez. The Lister Hill National Center for Biomedical Communications has been a major contributor to understanding natural language and medical images. The National Center for Biotechnology Information (NCBI) is an internationally recognized leader in providing biomedical and gene-related databases, from DNA sequences to genetic diseases, to a community of over 2 million Web users per day. The NCBI gathers basic research data on genomics and genetic variation and through an integrated set of databases helps to link basic science results to clinical practice.

In September 2004 the Secretary of the Department of Health and Human Services designated NLM as the central coordinating body for clinical terminology standards within the Department. In this role, NLM is the official depository and distribution center for clinical terminologies, responsible for integrating them within the UMLS Metathesaurus and for developing and maintaining mappings between designated standard clinical terminologies and important related terminologies, including the HIPAA code sets. In this role, NLM is also working to facilitate the alignment of terminology and messaging standards.

NLM works closely with the HHS Office of the National Coordinator for Health Information Technology (ONC) to ensure that NLM's efforts are aligned with the goal of the President and HHS Secretary for the nationwide implementation of an interoperable health information technology infrastructure to improve the quality and efficiency of health care.

Status and Next Steps

- *UMLS Knowledge Sources (http://umlsinfo.nlm.nih.gov/).* The Unified Medical Language System (UMLS) aims to facilitate the development of computer systems that behave as if they understand the meaning of biomedical and health terms. The UMLS Knowledge Source tools underpin many production information retrieval systems at NLM and elsewhere and are heavily used in advanced research in biomedical natural language processing and data-mining across the country and around the world. The most recent UMLS Metathesaurus contains more than 1.3 million biomedical concepts and 6.4 million concept names from more than 100 source vocabularies.

- *Clinical Vocabularies (http://www.nlm.nih.gov/healthit.html).* The UMLS Metathesaurus is a distribution mechanism for standard code sets and vocabularies used in health data systems. NLM supports, develops, or licenses key health terminologies to enable their free use in U.S. electronic health record systems. Three such key vocabularies are:

  – *SNOMED CT (http://www.nlm.nih.gov/snomed)* (Systematized Nomenclature of Medicine – Clinical Terms) is a comprehensive clinical terminology, originally created by the College of American Pathologists (CAP). In 2007 the International Health Terminology Standards Development Organisation (IHTSDO) was established to assume ownership, maintenance, and distribution of SNOMED CT in order to significantly promote global standardization of health information. NLM, on behalf of HHS, participated in the negotiations and is now the U.S. Member of the IHTSDO. This new organization will allow NLM, on behalf of the United States, to establish a new process for input to SNOMED CT development. In addition NLM will work with the IHTSDO to facilitate negotiations for the alignment and harmonization between SNOMED CT and key health terminologies including LOINC and RxNorm.

  – *RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/index.html),* developed by NLM, provides standard names for clinical drugs as expressed by a clinician for a patient and received by a pharmacy. RxNorm links its names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software. By providing links between these vocabularies, RxNorm can mediate messages between systems not using the same software and vocabulary. For example, RxNorm is being used by the Department of Defense (DoD) and Veterans Administration (VA) to facilitate the exchange of clinical drug information between the DoD Clinical Data Repository (which uses First DataBank) and the VA Health Data Repository (which uses NDF/RT). RxNorm is also being used in several epidemiologic investigations as a standard for coding drug exposures.

  – *LOINC (http://www.nlm.nih.gov/research/umls/loinc_main.html) (Logical Observation Identifiers Names and Codes)*, produced by the Regenstrief Institute, is a clinical terminology important for laboratory test orders and results providing universal identifiers for both laboratory and other clinical observations. NLM supports the ongoing development and distribution of LOINC through a contract arrangement with the Regenstrief Institute. Under the direction of the HHS Office of the Assistant Secretary for Planning and Evaluation, LOINC is being evaluated as a mechanism for standardized patient assessment instruments beginning with the nursing home Minimum Data Set (MDS). The expected outcome of this project is the ability for information exchange and re-use of content on federally sponsored assessments in an interoperable nationwide health information infrastructure.

- *Drug Label Inserts (http://dailymed.nlm.nih.gov/).* DailyMed, a joint project of the FDA and NLM, is an official distribution mechanism for FDA-approved packaging information (drug label inserts). Containing more than 3,000 labels, DailyMed links to other sources of drug information, including NLM's MedlinePlus, ClinicalTrials.gov, and PubMed. More than 60,000 people subscribe

to the DailyMed RSS data feeds. Additional labels will be added as annual updates to labels are received from pharmaceutical manufacturers and approved by the FDA.

- *Alignment of Terminology and Messaging Standards (http://www.nlm.nih.gov/healthit.html).* HL7 (Health Level Seven) is an ANSI-accredited Standards Development Organization creating messaging protocols to transfer clinical and administrative data between systems. HL7 is one of a suite of designated standards for use in U.S. Federal Government systems for the electronic exchange of clinical health information and is also a required standard in interoperability specifications of the Healthcare Information Technology Standards Panel (HITSP). In 2004, NLM contracted with HL7 to facilitate the alignment of HL7's messaging standards with key terminology standards. The focus of the contract is reviewing the terminology subsets identified for each messaging protocol and, where appropriate, replacing or enhancing the terminology subsets with standard terminologies (e.g., SNOMED CT; LOINC). The initial analysis will be completed in the fall of 2007.

- *Vocabulary Mapping Projects (http://www.nlm.nih.gov/healthit.html).* Health care providers must produce billing and statistical data using the HIPAA code sets. The use of standard clinical vocabularies will be more attractive and cost-effective if required HIPAA code set data can be generated from health care information recorded using standard clinical vocabularies. Toward this end NLM has the responsibility for funding, coordinating, and/or performing official mappings between standard clinical terminologies and HIPAA code sets. The first such map released for public review and comment is the draft LOINC to CPT (Current Procedural Terminology) map. Also under development are mappings between SNOMED CT and CPT as well as a mapping between SNOMED CT and ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification). Robust testing and validation procedures are under development.

- *Human Genetic Variation Information Resources (http://www.ncbi.nlm.nih.gov/).* Multiple databases available at NCBI contain information about genotypes and phenotypes, including PubMed and PubMed Central (the primary literature); Online Mendelian Inheritance in Man, or OMIM (allelic variant records); dbSNP (single nucleotide polymorphisms, small-scale insertions/deletions, polymorphic repetitive elements, and microsatellite variations); dbMHC (major histocompatibility complex data); and dbRBC (genetics of red blood cell antigens). NCBI's dbGaP (database of Genotype and Phenotype) has been designated the trans-NIH repository for Genome-Wide Association Studies. This database will contain NIH-supported clinical and longitudinal studies with high-density genotyping on the participants and associations between genetic markers and clinical traits. For each study, the database generally will include all the study documents, such as protocols and questionnaires, summary data for measured phenotype variables, summary data for genotype results, and de-identified individual-level genotype and phenotype data for each participant.

  The Collaboration, Education, and Test Translation (CETT) program is sponsored by NIH's Office of Rare Diseases (ORD) and provides funding and other support to move genetic tests from the research setting to clinical practice. In connection with the CETT program, clinical laboratories are beginning to supply NCBI with information about results of their genetic tests, including the reference sequences they use to test patients' DNA and de-identified test readouts and diagnoses.

  RefSeqGene is a reference sequence database specifically designed to provide a gene-specific genomic sequence for each human gene that is a target for genetic testing. RefSeqGene will provide a common language for communicating about variations in gene sequences, which is especially important when a gene has multiple splice variants or frequent mutations in nontranscribed regions.

- *Consumer Information Services.* Contributing to improved health literacy is a foundational goal for the NLM. NLM's consumer information services are heavily used by members of the public and by clinicians as aids to patient education. NLM resources providing genetic information for the consumer include:

  – *MedlinePlus (http://medlineplus.gov/)* (including MedlinePlus en español) is an award-winning resource providing the public with authoritative links to consumer health information on over 740 diseases and conditions. MedlinePlus combines authoritative information from numerous sources including the NIH, other government agencies, and health-related organizations. In addition, controlled vocabulary and system linkages are used to connect consumers to other NLM resources such as MEDLINE/PubMed, clinicaltrials.gov, Genetics Home Reference, and NIHSeniorHealth. MedlinePlus includes drug information written for the consumer as well as talking low-literacy tutorials on many key health issues such as diabetes, asthma, and arthritis. MedlinePlus includes several pages specifically discussing genetic information including Genes and Gene Therapy, Genetic Brain Disorders, Genetic Counseling, Genetic Disorders, and Genetic Testing. In 2007 MedlinePlus will deliver over a billion pages of health information.

  – *Genetics Home Reference (http://ghr.nlm.nih.gov/) (GHR)* provides basic information about genetic conditions and the genes and chromosomes related to those conditions. This online resource provides a bridge between the public's questions about human genetics and the rich technical data emerging from the Human Genome Project. Created for the general public, particularly individuals with genetic conditions and their families, the site currently includes summaries of more than 225 genetic conditions, more than 380 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA. On average, 10 new summaries are added per month. GHR's usage increased more than 60 percent in the past year, and the site is increasingly recognized as an important health resource.

Evaluation of Genomic Applications in Practice and Prevention

Centers for Disease Control and Prevention
http://www.egappreviews.org

Description

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) is a model project initiated in fall 2004 by the National Office of Public Health Genomics at the CDC. The project's goal is to support the first phases of a coordinated and systematic process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice. The EGAPP Project draws on existing recommendations for action in the United States and knowledge gained from other evaluative processes (e.g., U.S. Preventive Services Task Force, CDC-sponsored ACCE Project). The primary focus of the EGAPP project is an independent, non-Federal Working Group established in April 2005 and composed of 13 multidisciplinary experts in areas such as evidence-based review, clinical practice, public health, laboratory practice, genomics, epidemiology, economics, ethics, policy, and health technology assessment. Roles of the Working Group include developing methodology for review of genomic tests, selecting topics and defining key questions, analytic framework, and other criteria for each review, and then developing a recommendation on use of the test based on the completed report of available evidence.

Status and Next Steps

Four evidence reviews were commissioned to AHRQ Evidence-based Practice Centers, and two to other contractors:

- *Genomics Tests for Ovarian Cancer Detection and Management.* AHRQ report complete (http://www.ahrq.gov/clinic/tp/genovctp.htm); EGAPP Working Group Recommendation Statement expected in fall 2007.
- *Testing for Cytochrome P450 Polymorphisms in Adults with Non-Psychotic Depression Treated with Selective Serotonin Reuptake Inhibitors (SSRIs).* AHRQ report complete (http://www.ahrq.gov/clinic/tp/cyp450tp.htm); Recommendation Statement expected in fall 2007.
- *Hereditary Nonpolyposis Colorectal Cancer (HNPCC): Accuracy of Diagnostic Strategies and Implications to Patients with Colorectal Cancer and Their Families.* AHRQ report complete (http://www.ahrq.gov/clinic/tp/hnpcctp.htm); supplementary evidence review in progress and EGAPP Recommendation Statement expected in fall 2007.
- *Gene Expression Profiling for Breast Cancer Management and Prognosis.* AHRQ review in progress (http://www.ahrq.gov/clinic/tp/brcgenetp.htm).
- *Can UGT1A1Genotyping Reduce Morbidity and Mortality in Patients with Metastatic* Colorectal Cancer Treated with Irinotecan? Evidence report complete; EGAPP Working Group Recommendation Statement expected in fall 2007.
- *Use of Genomic Profiling to Assess Risk for Cardiovascular Disease and Identify Individualized Prevention Strategies.* Evidence review in planning.

Other key activities for the next year include collaborating with a range of partners (e.g., medical professional organizations, health plans, public health) to effectively disseminate evidence reports and recommendation statements, and surveying stakeholders to assess the usefulness of the products and potential impact of the information in practice.

Roadmap for Medical Research: Clinical and Translational Science Award Program

National Institutes of Health
http://nihroadmap.nih.gov/

Description

In 2002, NIH consulted extensively with its stakeholders, scientists, health care providers and the public to identify and prioritize the most pressing problems facing medical research that can be uniquely addressed by NIH as a whole. The NIH Roadmap for Medical Research was formulated after those initial consultations. Three broad themes emerged: New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise. The Roadmap lays out a vision for a more efficient and productive system of medical research, including more effective translation of research findings to clinical use.

Status and Next Steps

The Clinical and Translational Science Award (CTSA) program, led by NIH's National Center for Research Resources, brings together basic biomedical researchers and clinical investigators to address the critical need to accelerate the translation of basic biomedical research into new, more effective treatments for the American people.

CTSA-supported researchers, located at academic health centers across the Nation, will rapidly and efficiently transfer discoveries made in the laboratory into treatments for patients, including personalized approaches. For example, high-throughput equipment to describe the genetic characteristics of individuals is included in many CTSA sites. These technologies enable investigators to identify genes that predict how a patient will respond to drugs they are testing. Ultimately, this support will enable doctors to reduce the risk of adverse effects of medications as well as achieve the desired effects more rapidly.

The overall CTSA goal is to enable interdisciplinary teams to design new and improved clinical research informatics tools, forge new partnerships with private and public health care organizations, expand outreach to minority and medically underserved communities, develop better designs for clinical trials, and train the next generations of clinical and translational researchers. The CTSA awardees operate as a consortium so that expertise that is developed at one location can be shared with other sites, an important element of replicating approaches to personalized health care across the Nation.

This new consortium is the preeminent initiative to address the NIH Roadmap for Medical Research theme of Re-engineering the Clinical Research Enterprise. For more information, see www.ctsaweb.org.

Cancer Biomedical Informatics Grid (caBIG™)

National Cancer Institute, National Institutes of Health
https://cabig.nci.nih.gov/

Description

The cancer Biomedical Informatics Grid (caBIG™) initiative is accelerating research discoveries and improving patient outcomes by linking researchers, physicians, and patients throughout the cancer community. As we begin to better understand cancer at the molecular levels and personalized medicine is implemented in cancer patient care, researchers and clinicians will require more rapid access to—and easier methods to analyze—the multiple types of information involved. However, systems needed to help translate the necessary data into better patient outcomes are either nonexistent, disconnected, or underperforming. To this end, the vision of caBIG™ is a full cycle of integrated cancer research, extending from bench to bedside and back again.

Status and Next Steps

The caBIG™ community has developed and released a variety of bioinformatics tools and capabilities that span the entire continuum of clinical research, including genomics.

Tools:

- *The Clinical Data System (CDS)* is an independent and stand-alone data submission infrastructure (electronic) that serves as the primary data submission system for clinical trials. Data is submitted via a Web-based interface. The system also provides a mechanism for data access by stakeholders and enables users to view and generate reports about various aspects of the clinical trial process.

- *GoMiner*™ is a tool for biological interpretation of data from gene expression microarrays. These experiments often generate lists of dozens or hundreds of genes that differ in expression between samples, raising the question “What does it all mean biologically?”

Infrastructure:

- *caGRID™.* The goal of the cancer Biomedical Informatics Grid, caBIG™, is to develop applications and the underlying systems architecture that connects data, tools, scientists, and organizations in an open federated environment. In meeting this goal, caBIG™ will necessarily bring together data

from many and diverse data sources and support research into the understanding of individual differences in cancer risk. The underlying service-oriented infrastructure for caBIG™ is caGRID.

Examples of Datasets:

- *Cancer Genome Anatomy Project (CGAP).* This program has supported gene expression profiles of normal, precancer, and cancer cells, leading eventually to improved and customized detection, diagnosis, and treatment for the patient.
- *Cancer Molecular Analysis Project (CMAP).* CMAP enabled researchers to identify and evaluate molecular targets in cancer. The project provides molecular profiles, targets, targeted agents, and therapeutic trials to patient-specific disease applications.

The infrastructure and tools of caBIG™ are already widely applicable beyond the cancer community, and the initiative collaborates with health and biomedical information technology efforts in other domains. As caBIG™ continues to grow and more and more organizations become involved, caBIG™ will increasingly involve a cross-section of diverse users, contributors, and beneficiaries.

Promoting Quality in Genetic Testing

Clinical laboratories that perform waived, moderate and/or high complexity tests, including genetic tests, for patients are subject to quality standards and regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The CLIA program is administered by the CMS, with the technical support of the public health resources of the CDC, and in cooperation with the regulatory responsibilities for test categorization of the FDA. Most of the more than 1,000 genetic tests that are available today are categorized as high-complexity tests, and laboratories performing them are subject to the most stringent CLIA requirements, whether the tests are "kits" that have obtained premarketing approval from FDA, or laboratory-developed tests (LDTs), which are developed and utilized in-house by a single clinical laboratory.

CLIA quality standards generally apply to clinical laboratories for all non-waived tests on specimens derived from the human body for health assessment used in patient care. However, because of the rapid pace of development in genetic testing in particular, CMS and CDC are undertaking special steps to encourage the development of quality assurance tools and expertise in this area, including cooperative efforts with laboratories, professional organizations, subject matter experts, health care providers, and others. CMS has developed an Action Plan for Oversight of Genetic Testing, and CDC is carrying out efforts to improve availability of laboratory reference materials and to improve laboratory/clinician/consumer communications (see below).

In addition, a collaborative effort of Federal agencies, professional societies, advocacy organizations, academic institutes, industry, and other stakeholders has been assembled to improve the availability, accessibility, and quality of genetic testing for rare diseases. This effort led to, and has provided input to, the Collaboration, Education and Test Translation (CETT) program, which is supported by the ORD of the NIH to promote the translation of rare disease genetic tests from research phase to patient care (http://www.cettprogram.org).

The HHS Secretary has also solicited further advice from the Secretary's Advisory Committee on Genetics, Heath, and Society (SACGHS) regarding the full spectrum of genetic testing issues and future needs in the area. Findings and recommendations by the SACGHS are expected to be delivered early next year.

CLIA Oversight of Genetic Testing

Centers for Medicare & Medicaid Services
http://www.cms.hhs.gov/clia/

Description

The CMS Action Plan for Oversight of Genetic Testing, operating under current CLIA regulations, is focused on:

- The effective, targeted application of current regulations and authority.
- Working with other Federal agencies (especially CDC, FDA, and NIH) and professional associations to promote a comprehensive approach to genetic testing that includes more availability of proficiency testing (PT) materials and programs and alternatives for PT.
- Enhancing the expertise of surveyors and CMS in the area of genetic testing to better serve the community, and providing specific survey guidance to surveyors to assess compliance for these tests.
- Considering innovative alternatives for specialized survey of these laboratories and the review of their data.

Status and Next Steps

- Better protections for all testing:
  - 2003 Regulation: A final rule was issued by CMS in 2003 to strengthen the quality control requirements for all laboratories performing non-waived testing. The rule included some of the genetic testing recommendations made by the Secretary's Clinical Laboratory Improvement Advisory Committee (CLIAC).
  - Proficiency Testing for Genetic Tests: CMS will work with the CDC, FDA and the professional associations to promote the development of additional proficiency tests or alternative mechanisms for PT. Few proficiency tests currently exist for genetic tests due to a paucity of appropriate specimens and market concerns of PT providers and also because of the low utilization volumes of many of these tests.
  - Analytical Test Validation of Genetic Tests: CMS is obtaining assistance from CDC and FDA for evaluation of analytical test validation of LDTs.
- Better information and knowledge:
  - Guidelines: CMS will work with professional associations, such as the Clinical Laboratory Standards Institute and the American College of Medical Genetics (ACMG), to promote the development of consensus guidelines and educational materials on molecular and other genetic testing.
  - Coordination Among Federal Agencies: CMS is collaborating with CDC, FDA, the Federal Trade Commission (FTC) and NIH to ensure effective oversight of genetic tests and expand coordinated efforts toward future improvements. CMS has also enlisted the expertise of the CLIAC in this effort to develop guidance to facilitate CLIA compliance.
  - Information for Surveyors: CMS will issue an informational alert for State agencies and CMS regional offices to heighten the awareness of genetic testing and clarify that genetic testing

laboratories are subject to CLIA when tests are used to diagnose, prevent, assess or treat human illnesses and conditions. CMS will also seek to raise awareness in the research laboratory community of the need for laboratories to enroll in CLIA when genetic tests are used in patient care.

  - Training for Surveyors: CMS is exploring the development of a customized survey protocol to assess compliance in genetic laboratories where unique technologies and methodologies are utilized. This fall, CMS is providing surveyors with technical training on current technologies and the quality aspects of genetic testing by subject matter experts from the field.

  - CLIA Web Site Enhancement: CMS will coordinate with CDC to provide helpful educational genetic testing guidance and updates on its Web site for surveyors and laboratories.

- Better Monitoring and Enforcement:

  - Application of Existing Regulations: CMS will seek guidance from the CMS-approved accreditation organizations that already have specific molecular diagnostic standards through its Partners for Laboratory Oversight project. CMS will also work with state agencies, accrediting organizations and other Federal partners to promote the effective application of existing regulations to ensure that genetic testing is accurate and reliable; and will explore additional mechanisms to oversee these tests. When CMS becomes aware of a non-CLIA certified laboratory that is using the Internet to market, or is performing genetic testing for use in patient care, the agency will take swift action to address the CLIA deficiencies. CMS is maintaining a list and monitoring enrollment and performance of these direct-to-consumer laboratories.

  - Effective Communications: CMS will work with other Federal agencies, state agencies and accreditation organizations to accelerate the sharing of information about new developments in genetic testing, the existence of laboratories that have failed to register for CLIA, and enforcement actions. The CMS/CLIA Web site is being updated to reflect the certification status of all of the 200,000 laboratories enrolled in CLIA so that the public can utilize it when selecting a laboratory.

Promoting Effective Communication Between Laboratories and Clinical Settings

Centers for Disease Control and Prevention
http://www.cdc.gov/dls/genetics/

Description

The integration of knowledge about genomics into clinical and public health care services holds the promise of improving patient outcomes and promoting cost-effective use of resources. A key component to achieving this is the capacity to clearly communicate clinically relevant information derived from laboratory test results to those who make patient management decisions. Failure of health care providers to appropriately understand and apply test results can compromise both patient care and the capacity to achieve public health goals as related to the integration of genomics into health services. The Division of Laboratory Systems is charged with ensuring the quality of laboratory testing and takes a systems approach to assessing current practices and addressing shortcomings. In recognizing “effective communication” between the laboratory and clinical setting as an essential component to ensuring the quality of testing, an effort has been undertaken to understand current practices, collect evidence reflective of shortcomings, and find solutions. Working with the clinical and laboratory practice communities, a framework is in development that is anticipated to promote the effective communication of clinically relevant information between the laboratory and clinical settings important to clinical decision-making. The majority of the work has been

funded through cooperative agreement mechanisms in collaboration with professional organizations, laboratories, clinicians, payers, policymakers, and various Federal agencies.

Status and Next Steps

- *2002-2003.* Broad-based survey of laboratory directors and physicians asking about test reports, their format and perceptions of usefulness.
- *2003-2005.* Analysis of laboratory requisition forms and reports using cystic fibrosis as a model for DNA-based testing for heritable conditions.
- *2003.* National workgroup meeting to review findings and make recommendations for next steps.
- *2005.* Survey of obstetricians and gynecologists about their office practices and perceived satisfaction with report content.
- *2005.* Survey of clinical laboratories to determine practice patterns associated with ordering and reporting tests and results.
- *2005.* National workgroup meeting to review findings and make recommendations for next steps.
- *2006-2007.* Engagement of clinicians (pediatricians, obstetricians and gynecologists, and family practitioners) in workgroup settings to gather input to what constitutes an effective means to communicate test results from the laboratory (in terms of content and format of the report).
- *2007.* Preparing manuscripts to describe clinical and laboratory practice model derived from data collected, including candidate reports potentially useful for the reporting of molecular genetic results.
- *2007.* RFA (cooperative agreement) for "Reporting DNA-Based Genetic Test Results Applicable to Heritable Conditions and/or Markers of Drug Metabolism: The Clinical Laboratory Report as a Decision-Support Tool."

Genetic Testing Reference Materials Coordination Program

Centers for Disease Control and Prevention
http://wwwn.cdc.gov/dls/genetics/qcmaterials/

Description

Reference and quality control (QC) materials are essential for many aspects of genetic testing. These materials, which are tested alongside patient samples, allow the laboratories to detect errors due to test system failure or operator error. In addition, reference materials are needed for test development and validation, lot-testing of new reagent batches, and performance evaluation (PT/EQA programs). Over 1,100 genetic tests are currently offered in clinical laboratories; however, for the vast majority of these tests, no publicly available characterized reference or QC materials are available. In the absence of publicly available characterized reference and QC materials, laboratories must improvise to obtain these reagents and, in some cases, develop and run assays without adequate controls.

Status and Next Steps

The CDC has been involved for many years in efforts to develop appropriate and characterized reference materials for use by the genetics community. The Genetic Testing Reference Materials Coordination Program (GeT-RM) was established in partnership with the genetics community to ensure the quality of genetic testing by addressing the need for reference materials. The goal of this program is to coordinate a self-sustaining community process to improve the availability of appropriate and characterized materials for quality control, proficiency testing, test development, and research. This program helps the genetics community obtain appropriate and characterized reference materials, facilitate and coordinate

information exchange between users and providers of reference materials, and coordinate efforts for contribution, development, characterization, and distribution of reference materials for genetic testing. GeT-RM is coordinated by the CDC, but all of the actual work, including decisions about reference material priorities, specimen collection, material development, and characterization occurs through voluntary collaborations with laboratories in the genetics community.

GeT-RM has recently developed 57 characterized cell line-based reference materials for fragile X, disorders on the Ashkenazi Jewish Panel (Bloom syndrome, Canavan disease, Fanconi anemia, familial dysautonomia, Gaucher's disease, mucolipidosis IV, Neimann-Pick disease, and Tay-Sachs disease), cystic fibrosis, and Huntington's disease. These materials are (or will be) publicly available from Coriell Cell Repositories. A characterization study of 14 DNA materials with important mutations causing cystic fibrosis is currently under way in 6 clinical laboratories. Studies to characterize DNA materials with mutations in genes important for many of the disorders included in state newborn screening panels (including congenital adrenal hyperplasia, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease, cystic fibrosis, and galactosemia), additional mutations included in the Ashkenazi Jewish Panel (Gaucher, Tay-Sachs, Canavan) and several other disorders including inherited breast cancer (BRCA1 and 2), alpha-1 antitrypsin, and MEN2 will soon be initiated.

To date, the GeT-RM has focused its efforts on DNA-based testing for inherited genetic disorders. However, there is a similar lack of reference materials for other areas of genetics, including molecular oncology, molecular infectious disease testing, and biochemical genetic testing. To address these needs, GeT-RM, together with the genetics community, relevant professional organizations, and government agencies, is working to provide information about currently available reference materials for molecular oncology, molecular infectious disease, and biochemical genetic testing. Mechanisms to address reference material needs for these areas are also being considered.

Evidence-Based Practice

Effective Health Care Program
Agency for Healthcare Research and Quality
http://effectivehealthcare.ahrq.gov

Description

The Effective Health Care (EHC) Program conducts knowledge synthesis, new knowledge generation, and knowledge translation and dissemination for health care effectiveness research. These activities are coordinated by the AHRQ.

Status and Next Steps

- *Evidence-Based Practice Center (EPC) Program.* A network of 13 centers that focus on evaluation and synthesis of published evidence of effectiveness and comparative effectiveness of health interventions and in clarifying the gaps in knowledge. For example, a recent EPC report evaluated the effectiveness and safety of different treatment alternatives for gastroesophageal reflux disease (GERD).
- *Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Program.* A new network of 13 centers that focuses on rapid-turnaround research to inform gaps in the current research on health care interventions. These centers specialize in secondary data analysis but are also geared to perform primary data collection and analysis. Currently work includes developing best practices for use of registries to improve evidence on benefits and harms of medical innovations in practice, and conducting pilot studies that examine use of linked administrative data for surveillance for drug safety, in anticipation of CMS Part D data becoming available.

- *Eisenberg Clinical Decisions and Communication Science Center.* Focuses on communicating findings from the EHC program to effectively convey health care decisions to a wide variety of users. Part of this center's charge is communicating issues of risk to decision-makers (patients, providers, policymakers), including evaluating the potential risks and benefits of new medical technologies.

Through discussion with and extensive input from stakeholders, the Secretary of the Department of Health and Human Services chose 10 priority conditions to guide this work: arthritis and non-traumatic joint disorders; cancer; chronic obstructive pulmonary disease and asthma; dementia including Alzheimer's disease; depression and other mood disorders; diabetes mellitus; ischemic heart disease; peptic ulcer disease and dyspepsia; pneumonia; stroke and hypertension.

These conditions on the initial priority list are targeted to Medicare beneficiaries. Subsequent lists will include conditions relevant to the Medicaid programs and the State Children's Health Insurance Program (SCHIP). A further opportunity to suggest conditions for priority consideration is taking place in 2007.

Centers for Education and Research on Therapeutics

Agency for Healthcare Research and Quality and U.S. Food and Drug Administration

http://www.certs.hhs.gov/index.html

Description

The Centers for Education and Research on Therapeutics (CERTs) is a research program administered by the AHRQ, in consultation with the FDA, and agencies within the HHS. The mission of the CERTs is to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products.

Status and Next Steps

- *Evaluation of the Incremental Cost-Effectiveness of Long-Term Clopidogrel Therapy Following PCI.* Explore the economic implications of widespread adoption of evidence-based therapies for secondary prevention of coronary artery disease and heart failure from multiple perspectives.
- *Determination of Genetic Predictors of Drug-Induced QT Interval Prolongation.* Part of a collaboration with NIH/National Institute of General Medical Sciences Pharmacogenetics Network.
- *Consultation with the Coalition for Affordable Quality Healthcare (CAQH) on Their Cardiovascular Quality Initiative.* Collaborate with CAQH in developing a national initiative to evaluate long-term use of beta-blockers in patients with previous myocardial infarction.
- *Evaluation of the Impact of Heart Failure on the Medicare Program.* Predicting high-cost beneficiaries by developing a prediction rule to identify high-cost/high-risk heart failure patients.
- *Develop an Association of Working Conditions With Prescribing Errors in Primary Care.* The overall objective of this study is to evaluate the association of rates of risky prescribing events with both structural and functional characteristics of the primary care practices of two managed care organizations.
- *Estimating Odds Ratios Under Misclassification of the Outcome in a Large Database Cohort Study When Medical Records Are Sampled.* Large sample sizes are needed to study rare diseases and events; misclassification of the outcome is common and verification of all presumptive cases not feasible. The goal is to extend previously developed methodology by this group for adjustment for misclassification, which uses all or most exposed cases but only a

subsample of unexposed cases, to accommodate multivariable adjustment for cofounders and other covariates. The approach will be based on data-based weights applied in a logistic regression. A simulation study will be developed to examine the properties of the method.

Accelerating Change and Transformation in Organizations and Networks

Agency for Healthcare Research and Quality
http://www.ahrq.gov/research/ACTION.htm

Description

Often health services research findings are not implemented in practice and thus fail to improve the quality of health care Americans receive. With its program Accelerating Change and Transformation in Organizations and Networks (ACTION), AHRQ places the responsibility of investing in the implementation of good ideas, once proven, directly on those who produce, use, and fund such research. ACTION is a 5-year implementation model of field-based research that fosters public-private collaboration in rapid-cycle, applied studies. With a goal of turning research into practice, ACTION links many of the Nation's largest health care systems with its top health services researchers.

Status and Next Steps

Examples of Integrated Delivery System Research Network (IDSRN) or ACTION projects:

- *Managing and Evaluating Rapid-Cycle Process Improvements as Vehicles for Hospital System Redesign.* The objectives of this IDSRN project were to (1) develop structures and processes capable of coordinating and aligning approximately 50 rapid-cycle process improvement projects that will take place in a wide range of departments and units within Denver Health, (2) develop assessment (evaluation) methods and metrics for evaluating the implementation and impact of these projects, (3) provide timely feedback to project participants and to those charged with coordinating projects for the hospital as a whole and use this feedback to foster learning about rapid-cycle projects and the overall redesign effort, (4) use the evaluation methods and metrics to assess the overall contribution of these rapid cycle projects to hospital improvement and draw lessons for future efforts at hospital improvement and transformation at Denver Health and elsewhere, and (5) summarize and disseminate lessons learned from these projects at the microsystem level to achieve hospital-wide change (i.e., organization level) through coordinated microsystem change.

- *Patient Safety Analysis Training: A DoD/AHRQ Partnership.* The Department of Defense (DoD) Patient Safety Program with the Weill Medical College of Cornell University has extended collaboration between AHRQ and the DoD to develop a proper set of training curriculum modules to analyze medical error reports and data. This includes risk assessment, causal analysis, case-based reasoning, sense-making, and change implementation. The training curriculum is consistent with the Institute of Medicine 2004 report on patient safety. This IDSRN task order provides for services and material to translate a vast array of knowledge that has been attained in recent research regarding medical event reporting and bring it to bear within a rigorous, mature training program.

Practice-Based Research Networks

Agency for Healthcare Research and Quality
http://www.ahrq.gov/research/pbrn/pbrninit.htm

Description

Primary care practice-based research networks (PBRNs) involve practicing clinicians in asking and answering clinical and organizational questions about primary health care. The best of PBRN efforts link relevant clinical questions with rigorous research methods in community settings to produce scientific information that is externally valid and, in theory, assimilated more easily into everyday practice.

Increasingly, PBRNs are recognizing their potential to expand their purpose and are supporting quality improvement activities within primary care practices and the adoption of an evidence-based culture in primary care practice. Many PBRN leaders have begun to envision their networks as places of learning, where clinicians are engaged in reflective practice inquiries, and where clinicians, their patients, and academic researchers collaborate in the search for answers that lead to the improved delivery of primary care.

Status and Next Steps

In 2000, the United States had approximately 24 primary care PBRNs. AHRQ has since provided direct funding for more than 50 PBRNs through targeted grant programs and has provided technical and networking assistance for many more. In 2004, AHRQ research identified more than 110 primary care PBRNs operating across the United States. AHRQ further supports PBRNs through:

- *Annual PBRN Meeting.* AHRQ hosts a 3-day conference dedicated to advancing PBRN research through presentations, workshops, and networking. http://extranet.ahrq.gov/pbrn2006.
- *PBRN Resource Center.* A collaborative venture of Indiana University and the National Opinion Research Center (NORC), AHRQ's national PBRN Resource Center provides technical support to primary care PBRNs. The PBRN Resource Center includes:
  - Peer Learning Groups—ongoing group discussions among PBRN researchers, directors, and staff.
  - Electronic Repository of PBRN Research—An extensive, AHRQ-maintained database of research produced by primary care PBRNs.
  - PBRN Extranet—A secure, AHRQ-provided Web presence where the PBRN community can share within and beyond their individual networks.

NIH/NCRR will convene the second of two regional 1-day workshops to be held in Los Angeles, California, on September 21, 2007, to identify key barriers to and enablers of effective academic-community research partnerships and to develop and disseminate guidelines and best practices for conducting community-based clinical and translational research in minority communities and other medically underserved communities. The first regional 1-day workshop was held in conjunction with AHRQ's PBRN 2007 National Research Conference in Bethesda, Maryland, on May 15, 2007. The final products of these workshops will include recommendations to support NCRR initiatives to enhance clinical and translational research in underserved communities and leverage related efforts of sister agencies including AHRQ, HRSA, CDC, and the Indian Health Service.

Genetic Services Program

HRSA's genetic services program includes a broad range of clinical and public health activities, such as individual and community health assessment, genetic screening and counseling for inherited conditions, measuring susceptibility and prevalence of gene-related conditions that result from specific environmental exposures, and helping the population with genetic conditions manage their health. Currently, these and other services are provided in a variety of settings such as community health clinics, academic health centers, public health departments, public and private laboratories, and private health care providers. Through the funding of grants and cooperative agreements, the Agency's activities encompass the following program areas:

- The funding of public health infrastructure for the incorporation of new technology into newborn screening programs
- Funding of grants to examine emerging issues and technologies in newborn screening
- Training and education opportunities in newborn screening and genetics for health professionals
- Grants to encourage initiatives in genetic education for underserved populations
- Development of models for the delivery of genetic services, such as the National Hemophilia Program and thalassemia and sickle cell disease programs

These programs encourage the integration of various types of Federal, State, and community-funded newborn screening and genetics services into systems of care that are responsive to the individual needs of the people being served.

The HRSA Information Center offers a wealth of maternal and child health publications and resources. To see a complete list of offerings, visit www.ask.hrsa.gov or call toll-free (888) ASKHRSA (275-4772).

Genetic and Newborn Service Screening Regional Collaboratives

Description

In 2004, HRSA launched the establishment of regional genetic and newborn screening collaboratives to respond to the rapidly expanding and changing landscape of genetic and newborn screening services and the challenges in implementing those services; the increased need for subspecialists and "super" subspecialists to care for individuals identified through genetic testing as having rare disorders; and the geographic maldistribution of genetic and medical subspecialist expertise throughout the country. In partnership with the ACMG, HRSA has organized a National Coordinating Center (NCC) for these collaboratives (http://www.nccrcg.org/). The role of the NCC is to address issues of national importance and to facilitate inter-regional collaborations that move successful programs developed and incubated within regions to broader utilization by others that find them useful in meeting their own needs. The Center and the collaboratives conduct regional needs assessments for improving the health of children and families with genetic disorders, identifying barriers to genetic and newborn screening services, and working on issues that are relevant to improving services in their regions. This program provides future capabilities to conduct genetic research and clinical support for individualized approaches for interventions.

Status and Next Steps

Among the programs developed or developing within the NCC are materials such as the newborn screening ACT sheets (available at www.acmg.net) that support primary care professionals in accomplishing their own roles in genetic service delivery. Other programs are listed below.

- Developing disaster preparedness programs for newborn screening and genetics patients whose needs for ongoing care and treatment must be maintained during prolonged emergency situations.
- Working to directly involve the medical genetics community in the development of point-of-care educational content and clinical decision support tools for electronic medical record systems.
- Enhancing telegenetics capacity to extend the reach of genetics service providers into the local communities of their patients. This includes addressing barriers to such care delivery ranging from regulations/legislation that were developed with specific and much larger specialty groups than medical genetics in mind to the infrastructure needed to support the programs.
- Improving genetics education in medical schools.
- Developing national data collection programs for newborn screening patients and genetics patients, which is ongoing. The NCC is working with the Regional Collaboratives to develop long-term followup data collection programs for genetics patients identified through newborn screening programs. These efforts will assist the States in the evaluation and quality assurance of their newborn screening programs and provide a useful perspective on natural history of the treated condition and a patient resource for clinical trials of second-generation therapeutics. The ACMG and the NCC are working with the National Institute of Child Health and Human Development in the development of their National Newborn Screening Translational Research Network, a program that is directing research into new treatments and testing technologies for newborn screening as well as improving the evidence available at the national level on genetic diseases that may be candidates for newborn screening.

National Hemophilia Program

Description

The National Hemophilia Program was initiated in 1975 to develop a system of comprehensive services to persons with hemophilia and other bleeding disorders and their families. Currently 26 grantees are major hemophilia treatment centers that in turn support 124 affiliate and satellite centers through a regionalized system of care. Treatment centers are located in 44 States, the District of Columbia, and Puerto Rico.

The National Hemophilia Foundation (NHF) receives funds from HRSA and CDC to establish and conduct support activities in research, education, prevention, outreach, peer support, and professional education through a nationwide organization of affiliated chapters.

Status and Next Steps

The National Hemophilia Program has been built on the HRSA philosophy of family-centered, community-based, culturally competent, coordinated systems of care. Services provided through the regionalized network of treatment centers feature consumer participation, peer support, and self-help and include the following:

Comprehensive treatment for hemophilia provided through a multidisciplinary team, including services in genetic counseling, physical therapy, home infusion, orthopedic intervention, specialized dental services, psychosocial and peer support counseling, and financial counseling and assistance.

Sickle Cell Service Demonstration

Description

The Sickle Cell Service Demonstration Program was created in 2006 to develop mechanisms for the prevention and treatment of sickle cell disease, including the coordination of service delivery for individuals with sickle cell disease; genetic counseling and testing; bundling of technical services related to prevention and treatment of sickle cell disease; training of health professionals; and identifying and establishing other efforts related to the expansion and coordination of education, treatment, and continuity of care programs for individuals with sickle cell disease. Four regional Sickle Cell Disease Collaborative Networks (Networks) and a national coordinating center have been established under this demonstration program.

Status and Next Steps

Each Network supports the work, including service provision, education, genetic/hemoglobinopathy counseling, and outreach of three to five individual federally qualified health centers, nonprofit hospitals or clinics, and/or university clinics that provide primary care. The demonstration program is expected to increase the present capacity and capability of eligible ambulatory health care delivery entities to coordinate service delivery and genetic counseling and testing, and train health professionals in the care of individuals with sickle cell disease.

National Cord Blood Inventory

Description

The purpose of the National Cord Blood Inventory program is to provide funds to cord blood banks to build an inventory of the highest quality cord blood units for transplantation, which will be made available for transplantation through the C.W. Bill Young Cell Transplantation Program.

Blood stem cell transplants offer the possibility of a cure for people with leukemia and many other life-threatening blood disorders. Blood stem cells originally were obtained from the bone marrow of adult donors for these transplants (thus often referred to as bone marrow transplants; these cells now also may be obtained from the circulating blood of adult donors or collected from the newest source, the umbilical cord and placenta after a normal birth.

Most cord blood transplants have been performed for pediatric recipients, because of the smaller number of stem cells present in cord blood, and the effectiveness of cord blood transplants in pediatric patients is well established. Encouraging results in adult patients have been published in recent years; this may, especially if confirmed by ongoing studies, stimulate much wider use of cord blood transplants in adult patients over the next few years.

Because it can be used with a less perfect match in tissue type between the donor and recipient than is the case for adult donors, cord blood offers a chance of survival for patients who lack a suitably tissue-matched relative (only about 25 percent of patients have one) and who cannot find an adequately matched unrelated adult donor through the C.W. Bill Young Cell Transplantation Program (formerly the National Bone Marrow Donor Registry). Minority patients, especially African American patients, have a lower probability of finding a perfectly matched unrelated adult donor because of the greater diversity in their tissue types. Consequently, these patients are especially likely to benefit from additional cord blood units. In addition to their use in blood stem cell transplants, stem cells derived from cord blood can be used for clinical and preclinical research into a variety of cellular therapies.

Status and Next Steps

P.L. 109-129 establishes a target of 150,000 new, high-quality cord blood units for the National Cord Blood Inventory. Units in the National Cord Blood Inventory will be made available for blood stem cell transplants, and a portion of the other units collected by participating banks but not ultimately suitable for clinical transplantation will be made available for preclinical and clinical research focusing on cord blood stem cell biology and the use of cord blood stem cells for human transplantation and cellular therapies.

C.W. Bill Young Cell Transplantation Program

Description

The purpose of the C.W. Bill Young Cell Transplantation Program is to increase the number of transplants for recipients suitably matched to biologically unrelated donors of bone marrow and cord blood. Blood stem cell transplants offer the possibility of a cure for Americans suffering from leukemia and other blood and genetic diseases. Each year approximately 38,000 people younger than 55 years are diagnosed with these fatal illnesses, and about 16,000 of them cannot be successfully treated with therapy other than a blood stem cell transplant. When doctors have a patient in need of transplantation, they initially try to locate donors related to the patient. If none are available, as is the case for approximately 70 percent of patients, they need to search for a suitable unrelated donor.

The tissue types of marrow donors must be closely matched with those of their recipients in order for the transplant to be successful. Since tissue types are inherited, patients are more likely to find a closely matched donor within their own racial and ethnic group. However, because of the high rate of diversity in the tissue types of minorities, especially African Americans, the Program must continue to recruit donors from these groups to increase the possibility that patients will find a closely matched donor. For this reason, recruitment efforts under the Program emphasize increasing the number of minority volunteer donors.

Status and Next Steps

Per authorizing legislation signed on December 20, 2005 (The Stem Cell Therapeutic and Research Act of 2005, P.L. 109-129), the C.W. Bill Young Cell Transplantation Program is the successor to the National Bone Marrow Donor Registry. HRSA awarded contracts for a Cord Blood Coordinating Center, a Bone Marrow Coordinating Center, an Outcomes Database, and a combined Office of Patient Advocacy/Single Point of Access in FY 2006. P.L. 109-129 also required the establishment of an Advisory Council at the Department level. During FY 2007, all the components of the Program will be in place. While the scope of activities required of the Program are similar to that of the Registry, the Program has expanded responsibility of collecting, analyzing, and reporting on outcomes data for all allogeneic transplants and on other therapeutic uses of blood stem cells. In addition, unlike the Registry, which was administered under a single contract, the Program encompasses four contracts that require close coordination.

The Registry has steadily increased the number of transplants facilitated each year, from 2,205 in FY 2003 to 2,523 in FY 2004 to 2,688 in FY 2005. Despite this progress, candidates for unrelated donor transplants still outnumber recipients by approximately 5 to 1.

Newborn Screening Quality Assurance Program

Centers for Disease Control and Prevention
http://www.cdc.gov/nceh/dls/newborn.htm

Description

The Newborn Screening Quality Assurance Program is the only comprehensive source in the world for quality assurance and proficiency testing involving the testing of newborns for preventable diseases. If these diseases are not accurately diagnosed and treated, they cause mental retardation, severe illness, and (in some disorders) premature death in newborns.

Cystic fibrosis is a disorder that is rapidly being added to States' newborn screening panels. Often a two-tiered system is used. If the measurement of the biochemical target is elevated, it is confirmed by detecting mutations in the cystic fibrosis transmembrance conductance regulator gene. Based on the two results, babies who screen positive are sent for diagnostic testing. Proficiency testing programs for these laboratories are often required and are an important part of ensuring the quality of the laboratory and its methods.

Status and Next Steps

- A proficiency testing program using specimens that include both the biochemical target and the most common mutation was initiated in 2005 for newborn screening laboratories worldwide.
- A new proficiency testing program that tests laboratories' ability to detect many different cystic fibrosis mutations was initiated in February 2007. Specimens were acquired in collaboration with the University of Wisconsin School of Medicine and Public Health, Johns Hopkins Hospital, and Case Western University.
- This new program, the Cystic Fibrosis Mutation Detection Program, currently has 24 participants and is growing.
- We currently have a repository of 17 mutations and are continually adding more.
- CDC's Newborn Screening and Quality Assurance Program will continue to provide technical guidance and support for newborn screening laboratories.

Genetic Testing and Newborn Screening Disease Information Portal

Centers for Disease Control and Prevention
http://wwwn.cdc.gov/dls/genetics/default.aspx

Description

Since 2005, most States have expanded their newborn screening (NBS) programs to include the national uniform NBS panel recommended by the ACMG. As a result, there is an increased need by health care professionals and the public for information regarding diagnosis, genetic testing, intervention, and management of the disorders. However, the information available from current Web-based resources may often be fragmented or not easily accessible, thus causing the general public and other users substantial time and frustration searching over various sources for the desired information.

Status and Next Steps

- Enhancing information resources to provide easy-to-access, user-friendly information on genetic diseases, genetic tests, and testing services, not only for genetic professionals but also for primary care clinicians, patients and families, and other users, was one of the major recommendations from the October 2006 "Quality, Access, and Sustainability of Biochemical Genetic Testing" working meeting. This meeting was the third collaborative effort organized by CDC, ORD of the NIH, American Society of Human Genetics, ACMG, HRSA, Genetic Alliance, and several other key groups, to promote quality genetic testing in clinical and public health practice (http://wwwn.cdc.gov/dls/genetics/qualityaccess/default.aspx).

- Based on this recommendation, and recognizing that availability and accessibility of NBS information is an increasing public health need, CDC assessed the current Web-based resources for general disease information, genetic testing information, laboratories providing test services, testing algorithm, sensitivity and specificity of genetic tests, interpretation of test results, and disease management, for the 84 diseases on the ACMG-recommended NBS disease panel. A great degree of variability was found among the Web sites on the quality and extent of the information.

- Using the information compiled, a searchable database is developed to provide general practitioners, genetic specialists, laboratories, and the general public a central information portal to search for information on NBS diseases. It provides external links to publicly accessible resources, allowing streamlined, user-friendly searches on general disease information, specific genetic testing information, and disease management information, for each NBS disease. This information portal will be available for public access from the CDC Division of Laboratory Systems genetics Web site (http://wwwn.cdc.gov/dls/genetics/default.aspx) in August 2007.

Family History

U.S. Surgeon General's Family History Initiative
http://www.hhs.gov/familyhistory/

Description

To help focus attention on the importance of family history, the U.S. Surgeon General in cooperation with other agencies with the HHS has launched a national public health campaign, called the U.S. Surgeon General's Family History Initiative, to encourage all American families to learn more about their family health history.

Status and Next Steps

Americans know that family history is important to health. A recent survey found that 96 percent of Americans believe that knowing their family history is important. Yet, the same survey found that only one-third of Americans have ever tried to gather and write down their family's health history.

Because family health history is such a powerful screening tool, the Surgeon General has created a new computerized tool to help make it easy for anyone to create a sophisticated portrait of their family's health. The Web-based tool helps users organize family history information and then print it out for presentation to the family doctor. In addition, the tool helps users save their family history information to their own computer and even share family history information with other family members. The tool can be accessed at https://familyhistory.hhs.gov/.

As part of the effort to educate people about the importance of knowing their family health histories, in November 2006 the Surgeon General's Office announced two new HHS-funded outreach projects. Building

upon the foundation laid by the Surgeon General's Family History Initiative, NHGRI named two new Family History demonstration projects, focused on Alaska Native and urban Appalachian populations. The 1-year projects, each of which received $100,000, will develop community-based models to increase awareness among the public and health care professionals about the value of family history information in promoting health and preventing disease.

The NIH is developing a state-of-the-science conference on family history to review the current body of literature about how family history information is collected and what impact it has on the way patients are treated. The conference will probably be held in fiscal year 2009.

In addition, other HHS-funded efforts are encouraging State health departments to increase awareness about family history among health care providers and the general public. The CDC is funding the State health departments in Utah, Oregon, Minnesota, and Michigan to incorporate genomics into their health promotion and disease prevention activities. All four States are tying activities to the Surgeon General's initiative to increase awareness about family history among health providers and the general public.

Family History Public Health Initiative

Centers for Disease Control and Prevention
http://www.cdc.gov/genomics/activities/famhx.htm

Description

The Family History Public Health Initiative is a collaboration of Federal agencies, academia, State health departments, and health care organizations to evaluate how family history information can effectively be used to assess risk for common diseases and influence early detection and prevention strategies. Since beginning this initiative in 2002, CDC has completed the development of an innovative, Web-based tool, Family Healthware™, that collects information about health behaviors, screening tests, and family medical histories for six diseases: coronary heart disease, stroke, diabetes, and colorectal, breast, and ovarian cancer. CDC funded three research centers to conduct a clinical trial to evaluate the clinical utility of Family Healthware™. The study, consisting of approximately 4,000 patients who attend primary care practices, is measuring whether family history risk assessment, stratification, and personal prevention messages influence health behaviors and use of medical services.

Status and Next Steps

- The clinical trial of CDC's Family Healthware™ Web-based tool is scheduled for completion in late 2007. This tool is being evaluated for clinical use by the academic medical centers at the University of Michigan, Case Western Reserve University, and Evanston Northwestern Healthcare.
- CDC's Family Healthware™ formed the basis of the U.S. Surgeon General's "My Family Health Portrait," a successful collaboration between the Surgeon General's Office, NIH, CDC, and other HHS agencies. My Family Health Portrait is a Web-based tool that organizes family health information into a printed version that people can take to their health care professional to help determine whether they are at higher risk for disease.
- CDC developed a Web site of family history resources and tools, including factsheets, case studies, news articles, and other resources, to facilitate the use of family history for health promotion. (http://www.cdc.gov/genomics/public/famhistMain.htm).

V. Privacy and Other Issues

Protecting the Privacy of Patient Health Information

HHS Office for Civil Rights
http://www.hhs.gov/ocr/hipaa

Description

Compliance with the first-ever comprehensive Federal privacy standards to protect patients' medical records and other health information provided to health plans, doctors, hospitals, and other health care providers was required on April 14, 2003 (April 14, 2004, for small health plans). Developed by HHS, these standards provide patients with access to their medical records and more control over how their personal health information is used and disclosed. They represent a uniform, Federal floor of privacy protections for consumers across the country. The standards, created pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA), are enforced by HHS's Office for Civil Rights.

Status and Next Steps

HIPAA included provisions designed to encourage electronic transactions and also required new safeguards to protect the privacy and security of health information. Through its Office for Civil Rights, HHS has conducted extensive outreach and provided guidance and technical assistance to providers and businesses to make it as easy as possible to implement the Privacy Rule. These efforts include answers to hundreds of common questions about the rule, as well as explanations and descriptions about key elements of the rule. These materials are available at http://www.hhs.gov/ocr/hipaa.

The Privacy Rule promotes a national floor of privacy protections for patients by limiting the ways that covered health plans, pharmacies, hospitals, and other covered entities can use and disclose patients' personal medical information. The regulations protect medical records and other individually identifiable health information held by covered entities, whether it is on paper, in computers, or communicated orally. Key provisions of these standards include:

- *Access to Medical Records.* Patients generally should be able to see and obtain copies of their medical records and request corrections if they identify errors and mistakes.
- *Notice of Privacy Practices.* Covered health plans, doctors, and other health care providers must provide a notice to their patients regarding how the covered entity may use personal medical information and the patients' rights under the Privacy Rule.
- *Limits on Use and Disclosure of Individually Identifiable Health Information.* The Privacy Rule sets limits on how health plans and covered providers may use and disclose individually identifiable health information. To promote the best quality care for patients, the Privacy Rule does not restrict the ability of doctors, nurses, and other providers to share information needed to treat their patients.
- *Prohibition on Marketing.* The Privacy Rule sets restrictions and limits on the use of patient information for marketing purposes.
- *Confidential Communications.* Under the Privacy Rule, patients can request that their doctors, health plans, and other covered entities take reasonable steps to ensure that their communications with the patient are confidential.
- *Complaints.* Consumers may file a formal complaint regarding the privacy practices of a covered health plan or provider. Such complaints can be made directly to the covered provider or health

plan or to the HHS Office for Civil Rights (OCR), which is charged with investigating complaints and enforcing the privacy regulation. Information about filing complaints should be included in each covered entity's notice of privacy practices. Consumers can find out more information about filing a complaint at http://www.hhs.gov/ocr/hipaa or by calling (866) 627-7748.

The Privacy Rule requires covered health plans, pharmacies, doctors, and other covered entities to establish policies and procedures to protect the confidentiality of protected health information about their patients. These requirements are flexible and scalable to allow different covered entities to implement them as appropriate for their businesses or practices.

Secretary's Advisory Committee on Genetics, Health, and Society

http://www4.od.nih.gov/oba/sacghs.htm

Description

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) serves to (1) provide a forum for expert discussion and deliberation, (2) assist HHS and other Federal agencies (at their request) in exploring issues raised by the development and application of genetic technologies, and (3) make recommendations to the Secretary on solutions. The SACGHS explores, analyzes, and presents options on the broad range of policy needs associated with the scientific, clinical, public health, ethical, economic, legal, and social issues raised by the development, use, and potential misuse of genetic and genomic technologies.

Status and Next Steps

The SACGHS has made a number of recommendations to the Secretary regarding:

- Coverage and reimbursement of genetic tests
- Genetic discrimination
- Direct-to-consumer marketing of genetic tests
- Genetics education for health professionals
- Health information infrastructure
- Surgeon General's Family History Initiative
- Large population studies

The SACGHS is currently addressing a wide variety of topics, including oversight of genetic testing, pharmacogenomics, and gene patents and licensing practices.

National Committee on Vital and Health Statistics

http://ncvhs.hhs.gov

Description

The National Committee on Vital and Health Statistics (NCVHS) is the statutory public advisory committee on health information policy to the Secretary of HHS. The Committee, first chartered in 1949, is composed of 18 individuals from the private sector who have distinguished themselves in the fields of health statistics, electronic interchange of health care information, privacy and security of electronic information, population-based public health, purchasing or financing health care services, integrated computerized health information systems, health services research, consumer interests in health information, health data standards, epidemiology, and the provision of health services.

Status and Next Steps

The NCVHS has delivered dozens of letter reports to the Secretary, including recent recommendations on:

- Data Linkages To Improve Health Outcomes
- Privacy issues in the Nationwide Health Information Network (NHIN)
- Functional requirements for the NHIN
- Improvements to data on race, ethnicity, and language
- Personal health records and systems
- Data standards for health information
- Quality measurement
- Lessons learned from the first 10 years of HIPAA

The NCVHS is currently addressing a wide variety of topics, including secondary uses of health data in the NHIN, individual control of sensitive information in the NHIN, the National Provider Identifier, HIPAA streamlining, and performance measurement and quality improvement.

Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

http://mchb.hrsa.gov/programs/genetics/committee/

The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC) was established to assist the Secretary of HHS by providing:

- Advice and recommendations concerning the grants and projects authorized under the Heritable Disorders Program.
- Technical information to develop policies and priorities for this program that will enhance the ability of the State and local health agencies to provide for newborn and child screening, counseling and health care services for newborns and children having or at risk for heritable disorders.

The Committee advises and guides the Secretary regarding the most appropriate application of universal newborn screening tests, technologies, policies, guidelines and programs for effectively reducing morbidity and mortality in newborns and children having or at risk for heritable disorders.

OVERVIEW OF FEDERAL HEALTH CARE DELIVERY PROGRAMS

The Department of Veterans Affairs (VA), Department of Defense (DoD), and Indian Health Service (IHS) are the three primary Federal health care providers. They have led innovation in the development of electronic health records, personal health records, and effectiveness and outcomes research.

Department of Veterans Affairs

Veterans Healthcare System Mission

http://www.va.gov/

The mission of the Veterans Healthcare System (VHA) is to serve the needs of America's veterans by providing primary care, specialized care, and related medical and social support services. To accomplish this mission, VHA needs to be a comprehensive, integrated health care system that provides excellence in health care value, excellence in service as defined by its customers, and excellence in education and research, and needs to be an organization characterized by exceptional accountability and by being an employer of choice.

Veterans Health Information Systems and Technology Architecture

http://www.va.gov/vista_monograph/

The VA has had automated information systems in its medical facilities since 1985, beginning with the Decentralized Hospital Computer Program information system, including extensive clinical and administrative capabilities. The Veterans Health Information Systems and Technology Architecture (VistA), supporting ambulatory and inpatient care, delivered significant enhancements to the original system with the release of the Computerized Patient Record System (CPRS) for clinicians in 1997. CPRS provides a single interface for health care providers to review and update a patient's medical record and to place orders, including medications, special procedures, x-rays, patient care nursing orders, diets, and laboratory tests. CPRS is flexible enough to be implemented in a wide variety of settings for a broad spectrum of health care workers and provides a consistent, event-driven, Windows-style interface.

My HealtheVet (online gateway to veteran health benefits and services)

http://www.myhealth.va.gov/#about-mhv

My HealtheVet (MHV) is a Web-based application that creates a new, online environment where veterans, family, and clinicians may come together to optimize veterans' health care. Web technology combines essential health record information enhanced by online health resources to enable and encourage patient/clinician collaboration. It is the first Web-based application created by the Office of Information for veterans, and can even be used by non-veterans with Web access to create a personal health record.

MHV provides one-stop shopping for information on VA benefits, special programs, and health information and services. MHV also provides services and tools to enable veterans to increase their knowledge about health conditions, better record their health status and communicate with their care providers, and become better-informed participants in improving their health. Veterans can now partner with their clinicians to gain a better understanding of their health status and take a more active role in self-management and shared health care decision-making.

Clinical Science Research and Development
http://www.research.va.gov/programs/csrd/default.cfm

Clinical Science Research and Development (CSR&D) supports research focusing on intact human beings as the unit of examination. Examples include interventional and effectiveness, clinical, epidemiological, and technological studies.

Department of Defense

Military Health System
http://www.ha.osd.mil/

Military Health System Mission (http://www.ha.osd.mil/)

Sustaining a medically ready military force and providing world-class health services for those injured and wounded in combat remain the primary mission of the Military Health System (MHS). As we continue to seek ways to improve the health care for our beneficiaries, we constantly explore new avenues of partnership with the VA and strive to improve access to care throughout the care continuum.

From a clinical information technology perspective, the MHS vision includes the achievement of complete interoperability with the VA and the provision of full access to the patient record for each beneficiary.

AHLTA (the military's electronic health record, http://www.ha.osd.mil/AHLTA/)

Since its initial deployment of stand-alone medical information systems to major military hospitals in 1981, the MHS has continued to improve its automated information systems with the goal of improving information access in support of timely, high-quality care delivery. For more than a decade, the MHS used one of the world's largest Computerized Provider Order Entry systems to capture important patient information for its more than 9 million beneficiaries. Known as the Composite Health Care System, the DoD's initial enterprise-wide health record system made the technological leap from paper to electronic order entry. Building upon that success, the DoD implemented AHLTA, DoD's comprehensive, global EHR and clinical data repository (CDR).

AHLTA is a secure, standards-based, and patient-centric EHR for use in garrison-based medical facilities and forward-deployed medical units. AHLTA provides military physicians with decision support and builds a single encounter document from a team effort, linking diagnoses, procedures, and orders into one record. AHLTA creates a lifelong, computer-based patient record for each and every military health beneficiary, regardless of location, and provides seamless visibility of health information across the entire continuum of medical care. This gives military providers unprecedented access to critical health information whenever and wherever care is provided to our service members and beneficiaries.

AHLTA offers clinical reminders for preventive care and clinical-practice guidelines for those with chronic conditions. AHLTA significantly enhances the MHS's effort to create healthy communities and increase patients' personal engagement in their own health care.

DoD's Clinical Data Repository centrally stores patient health care history for all MHS beneficiaries. The CDR is fully operational and contains electronic clinical records for more than 9 million beneficiaries. Its associated Health Data Dictionary normalizes the data creating a single record per patient worldwide, giving DoD an enterprise-wide view of the data. AHLTA captures coded symptom and physical finding-level data using a MEDCIN® medical terminology engine. This facilitates data mining and public health reporting capabilities and military readiness. Data synchronization service keeps the central repository up to date. The Clinical Data Repository plays a critical role in the exchange of computable clinical information between the

DoD and the VA and the data mediation, mapping, and terminology services required for the exchange of computable information.

TRICARE Online (patient Web portal, https://www.tricareonline.com/preloginHome.do)

TRICARE Online (TOL) is the Military Health System (MHS) portal for secure access to applications and services for beneficiaries, providers, staff, and external support contractors. TOL improves access to health care services and benefits and provides high-quality health care information from trusted sources.

Using TOL, beneficiaries can schedule appointments online via a secure Internet site; access is provided to 18 million pages of general health information, including symptoms and treatment options for children, automated tools for checking medications for possible adverse reactions and creating a personal health journal, and details on specific MHS services and benefits.

TOL services for providers include viewing and printing a patient's pre-and-post deployment forms, and MTFs can process, route, review, and authorize nonavailability statements. TOL also gives providers remote secure access to the Composite Health Care System resources as well as a 24/7 interactive Web-based training module based on their specific roles within TOL. Security and authentication benefits of TOL include a single sign-on solution for all Web applications used by MHS staff.

Indian Health Service
www.ihs.gov

Resource and Patient Management System
www.ehr.ihs.gov
www.ihs.gov/cio/rpms

The IHS is the principal Federal health care provider and health advocate for Indian people and provides a comprehensive health services delivery system for American Indians and Alaska Natives. The range of services includes traditional inpatient and ambulatory care, preventive care, and population health, delivered through a network of hospitals and clinics distributed through 35 States. IHS has long been a pioneer in using computer technology to capture clinical and public health data. The IHS clinical information system is called the Resource and Patient Management System (RPMS). The RPMS has been the health information solution for IHS since the early 1980s and comprises an integrated suite of over 60 clinical, administrative, financial, and infrastructure applications. RPMS provides the data that inform individual patient care, assesses quality of care and the health status of communities, and enables reporting on the performance of the IHS mission. Its development began nearly 30 years ago, and many facilities have access to decades of personal health information and epidemiological data on local populations. In recent years, IHS has been deploying enhancements to RPMS to achieve full electronic health record (EHR) capabilities, including a graphical user interface, electronic provider order entry, electronic note authoring, and imaging.

Clinical Reporting System
http://www.ihs.gov/cio/crs/

Clinical Reporting System (CRS) is the reporting tool used by the IHS Office of Planning and Evaluation to collect and report clinical performance results annually to HHS and to Congress. CRS is an RPMS software application designed for national reporting as well as local and area monitoring of clinical performance measures. CRS produces on demand from local RPMS databases a printed or electronic report for any or all of over 300+ clinical performance measures, representing 55 clinical topics. CRS is intended to eliminate the need for manual chart audits for evaluating and reporting clinical measures that depend on RPMS data.

GLOSSARY OF TERMS

(For a complete list, see the National Human Genome Research Institute's "Talking Glossary" at http://genome.gov/10002096.)

Biomarkers: Biological parameters associated with the presence and severity of specific disease states. Biomarkers are detectable and measurable by a variety of methods including physical examination, laboratory assays, and medical imaging.

Genome: All the genetic information possessed by an organism.

Genomics: The study of this genetic information.

Genotype: The genetic identity of an organism.

Genome-Wide Association Studies: An approach that involves rapidly scanning markers across an individual's genome, to find genetic variations associated with a particular disease. Once new genetic targets are identified, researchers can use the information to develop better strategies to detect, treat, and prevent the disease.

Health informatics, or medical informatics: The intersection of information science, medicine, and health care. It deals with the resources, devices, and methods required to optimize the acquisition, storage, indexing, retrieval, and use of information in health and biomedicine. Health informatics tools include not only computers but also clinical guidelines, formal medical terminologies, and information and communication systems.

Microarray technology: A new way of studying how large numbers of genes interact with each other and how a cell's regulatory networks control vast batteries of genes simultaneously.

Personalized health care: Describes medical practices that are targeted to individuals on the basis of their specific genetic code in order to provide a tailored approach. These practices use preventive, diagnostic, and therapeutic interventions that are based on genetic tests and family history information. The goal of personalized health care is to improve health outcomes and the health care delivery system as well as the quality of life of patients everywhere.

Pharmacogenomics: The study of how variations in the human genome affect an individual's response to medications.

Phenotype: The observable traits or characteristics of an organism, for example, hair color, weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.

HHS AGENCIES AND WEB SITES

AHRQ – Agency for Healthcare Research and Quality
http://www.ahrq.gov/

CDC – Centers for Disease Control and Prevention
http://www.cdc.gov/

CMS – Centers for Medicare & Medicaid Services
http://www.cms.hhs.gov/

FDA – U.S. Food and Drug Administration
http://www.fda.gov/

HRSA – Health Resources and Services Administration
http://www.hrsa.gov/

IHS – Indian Health Service
http://www.ihs.gov/

NIH – National Institutes of Health
http://www.nih.gov/

- National Cancer Institute (NCI)
  http://www.cancer.gov/
- National Eye Institute (NEI)
  http://www.nei.nih.gov/
- National Heart, Lung, and Blood Institute (NHLBI)
  http://www.nhlbi.nih.gov/index.htm
- National Human Genome Research Institute (NHGRI)
  http://www.genome.gov/
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
  http://www.niaaa.nih.gov/
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
  http://www.niams.nih.gov/
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
  http://www2.niddk.nih.gov/
- National Institute of General Medical Sciences (NIGMS)
  http://www.nigms.nih.gov/
- National Institute of Neurological Disorders and Stroke (NINDS)
  http://www.ninds.nih.gov/
- National Library of Medicine (NLM)
  http://www.nlm.nih.gov/

OCR – Office for Civil Rights
http://www.hhs.gov/ocr/

ONC – Office of National Coordinator for Health Information Technology
http://www.hhs.gov/healthit/onc/mission/

SAMHSA – Substance Abuse and Mental Health Services Administration
http://www.samhsa.gov

HHS-SUPPORTED WEB SITES OF INTEREST

HHS supports numerous Web sites, ranging from basic background information to clinical and research tools, in the areas relevant to Personalized Health Care, especially genomics. Below are leading sites for more information. (Web sites for specific agencies or programs are included in the text of the report.)

Personalized Health Care – Policy and Practice

HHS Secretarial Initiative on Personalized Health Care
http://www.hhs.gov/myhealthcare/

Surgeon General's Family History Tool
http://www.hhs.gov/familyhistory/

Online Course for Physicians – Genetics and Medicine (*prepared jointly with FDA)
http://ama.learn.com

National Coalition for Health Professional Education in Genetics
http://www.nchpeg.org/

Bioethics
http://bioethics.od.nih.gov/

Genetics and Genomics – Background

Genomics Primer
http://www.ncbi.nlm.nih.gov/About/primer/

Genetics Home Reference
http://ghr.nlm.nih.gov/

Genes and Gene Therapy - MedlinePlus
http://www.nlm.nih.gov/medlineplus/genesandgenetherapy.html

Genes and Disease
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=gnd.TOC&depth=1

Understanding the Human Genome Project
http://www.genome.gov/25019879

Cancer Genetics Overview
http://www.cancer.gov/cancerinfo/pdq/genetics/overview

Genetic and Rare Diseases Information Center
http://rarediseases.info.nih.gov/html/resources/info_cntr.html

Genetic Tools and Medical Care

Gene Tests
http://www.genetests.org/

Medicines for You: Studying How Your Genes Can Make a Difference
http://publications.nigms.nih.gov/medsforyou/

Pharmacogenomics
http://www.ornl.gov/hgmis/medicine/pharma.html

FDA Genomics Web Site
www.fda.gov/cder/genomics

NIH PharmGKB
http://www.pharmgkb.org/

Centers for Disease Control and Prevention
http://www.cdc.gov/genomics/public.htm

- Genomics and Disease Prevention
  http://www.cdc.gov/genomics/
- Six Weeks to Genomic Awareness
  http://www.cdc.gov/genomics/training/sixwks.htm
- Genomics and Health Weekly Update
  http://www.cdc.gov/genomics/update/current.htm

Research Information Tools

ClinicalTrials.gov – National Institutes of Health
http://clinicaltrials.gov/

PubMed Central
http://www.pubmedcentral.nih.gov/

NHANES III Genetics Information
http://www.cdc.gov/nchs/about/major/nhanes/nh3data_genetic.htm

National Center for Biotechnology Information
http://www.ncbi.nlm.nih.gov/

- Genes and Disease (NCBI Bookshelf)
  http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/gnd/tocstatic.html
- OMIM, Online Mendelian Inheritance in Man
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
- PubMed: Clinical Queries: Medical Genetics Searches
  http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml#medgen
- GenBank
  http://www.ncbi.nlm.nih.gov/Genbank/index.html

- Genome Resources
  http://www.ncbi.nlm.nih.gov/genome/guide/human/resources.shtml
- Database of Single Nucleotide Polymorphisms (SNPs)
  http://www.ncbi.nlm.nih.gov/SNP/index.html
- DNA and Clinical Data Related to Major Histocompatibility Complex (MHC)
  http://www.ncbi.nlm.nih.gov/mhc/MHC.cgi?cmd=init
- dbGAP
  http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap

NHLBI Resequencing and Genotyping
http://rsng.nhlbi.nih.gov/scripts/index.cfm

Medical Evidence, Effectiveness, and Quality

National Guideline Clearinghouse
http://www.guideline.gov/

National Health IT Resource Center
http://healthit.ahrq.gov

U.S. Preventive Services Task Force
http://www.ahrq.gov/clinic/uspstfix.htm

Guide to Community Preventive Services
http://www.thecommunityguide.org/

U.S. Department of Health and Human Services
Personalized Health Care Initiative
http://www.hhs.gov/myhealthcare/