President's Council of Advisors on Science and Technology (PCAST)

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Proposal to Study Personalized Medicine

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How Effective are Most Drugs?

- **Response rates (Efficacy Rate) of patients to a major drug in selected therapeutic area[1]:**

Analgesic (Cox-2):	**80%**
Asthma:	**60%**
Depression (SSRI):	**62%**
Diabetes:	**57%**
Oncology:	**25%**
Osteoporosis:	**48%**
Rheumatoid Arthritis	**50%**

[1]Spear, et al, Trends in Molecular Medicine, 2001; 7: 201-204.

Personalized Medicine—Background

- ***Personalized Medicine*** is the practice of tailoring medical treatments for patients based upon their individual responses to specific drugs. Drug response information arises from:

- ***Pharmacogenomics***: the study of genes that cause differences in responses to drugs;

- ***Pharmacogenetics***: the study of the individual inherited genetic variation in drug metabolism and response.

   (These terms are often used interchangeably today.)

Personalized Medicine—Background

- **Increasing evidence that genetic variations in individuals cause differences in drug reactions, such that:**
    1. **Some experience toxicities to dosages appropriate for others and/or**
    2. **Some process drugs too quickly for their intended benefit.**

- **Evidence currently exists for polymorphisms (genetic variants that appear in at least 1% of the population) causing different responses to a wide range of drugs, including[1]:**

    cholesterol lowering drugs and beta-blockers (heart disease); bronchodilators (asthma); chemotherapeutics (cancer); levodopa, dopamine and serotonin reuptake inhibitors (mental disorders) and anticoagulants (stroke).

- **Can drug responses caused by inherited genetic differences be quantified/correlated to justify (for safety or efficacy) diagnostic testing of individuals prior to their receiving a specific drug prescription or treatment?**

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1. Robertson, et al, Health Affairs, Vol. 21, Number 4, 2002.

Personalized Medicine—Background

- **Herceptin—Treatment of HER2 positive breast cancer;**

- **Gleevec—Treatment of adults with newly diagnosed, Philadelphia chromosome-positive chronic myeloid leukemia;**

- **Iressa—Treatment of non-small cell lung cancer with recent emphasis on patients having specific tyrosine kinase mutations in the EGFr gene;**

- **HIV– Therapy tailored by series of biomarkers (e.g. CD4, HIV-1 RNA);**

- **Amplichip Cytochrome P450—Measures cytochrome mutations in patients' DNA responsible for drug responses to antidepressants, antipsychotics, beta-blockers and some chemotherapeutics.**

Personalized Medicine—Potential Benefits

- ***Patients***: optimize efficacy, minimize side-effects, reduce medical costs;

- ***Product (Drug and Diagnostic) Developers***: reduce development costs, speed approvals, identify non-responders and create new markets, "rescue" of selected failed drugs, reduce liability with more accurate labeling, reduce/eliminate recalls;

- ***Regulators:*** increase sensitivity, specificity and positive predictive value to simplify oversight of validity and utility of diagnostic tests, enhance safety and efficacy of treated patient populations to simplify initial oversight of therapies, as well as long-term, post-marketing surveillance;

- ***Payers/CMS***: testing becomes "gatekeeper" to therapy, reduce direct/indirect costs of ineffective/harmful treatments, optimize allocation of resources.

Personalized Medicine—Challenges[1]

- *Patients*: informed consent, access/privacy of genetic information, legal protection for unauthorized disclosure, individual and societal comfort/concerns with testing, education, "gatekeeping" of desired treatments;

- *Product (Drug and Diagnostic) Developers*: narrowing of therapeutic markets/products, conflicts over who creates and manufactures tests, potential for regulatory delays with complex tests/therapies, disincentive for innovation for increasingly smaller markets;

- *Regulators:* greater demands to police "home brew" reagents and related diagnostic testing, increase federal standards for laboratory proficiency, determination of labeling for new therapies relative to advisability of diagnostic tests and related potential drug responses associated with specific genotypes;

- *Payers*: acceptance and funding of tests and related prescriptions, testing requirement prior to therapy/coverage, adoption of "gatekeeper" or "modified gatekeeper" model for practice;

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1. Robertson, et al, Health Affairs, Vol. 21, Number 4, 2002.

PCAST's Challenge

What perspective can PCAST contribute to the President (and different agencies) about the private sector's advancements in Personalized Medicine?

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■ *Big Picture*

    ➔ What is the excitement with PM?

    ➔ How real is it today?

    ➔ Does this field hold the potential to inspire and elevate STEM education/research?

    ➔ Does this field hold the potential to help control or escalate health care costs and associated quality and delivery?

    ➔ What are the potential roles of the private sector and public sector in forwarding PM?

PCAST—Proposal to Study Personalized Medicine

** Highlight one-day conference to educate policymakers **

I. **Overview and Introduction—The Potential and Promise of Personalized Medicine**

II. **Personalized Medicine in Practice Today :**

- **Two industry speakers to discuss the development and launch of Gleevec, Herceptin and/or Iressa;**

- **Industry speaker representing approved diagnostic tests—What is the current evidence that selective diagnostic tests provide sufficient positive predictive value to gain regulatory approval and market acceptance?**

- **Two academic medical personnel to discuss the practice of tests and related therapies.**

Panel Discussion: all speakers.

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One-Day Conference, Continued

III.   **Personalized Medicine Research and Development**

- **Director of one of the "Genome Institutes"—Where does the genome project end and PM begin? What is state-of-the-art speed/costs of genetic/genomic analysis?**

- **Directors of Genome-Clinical Institutes—Why have such centers been established? What is the role of academic institutions in bringing PM to medicine? What are the impediments to bringing PM to patients?**

- **IT/Genome/PM Expert—Speaker to describe and discuss the state of information technology as it relates to PM;**

- **HHS representative—What is the state of the electronic medical record/personal health record and other government healthcare IT activities, as they relate to the evolution of PM?**

Panel Discussion: all speakers.

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One-Day Conference, Continued

IV. **Stakeholder Perspectives on the Future of PM**
   - **Two Pharmaceutical/Biotech representatives (one with products/markets to protect and one without)—How is PM changing the nature and structure of drug research? What are the new risks/rewards to pharma development introduced by PM?**
   - **Diagnostic representative—Will the historical development/reimbursement paradigm work for PM diagnostic products?**
   - **HMO or large provider—Who is participating? When is the payoff?**
   - **Venture Capital spokesperson—What is the investment? When do we see returns?**
   - **Private Payer—Will costs escalate or decline? When?**

Panel Discussion: All speakers.

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One-Day Conference, Continued

v. **Policy Implications for Education/Training and the Individual Patient**

- **Personalized Medicine trade association representative—What are the privacy and ethical issues?**

- **Physician representative—How/when do we change physician education and training?**

- **Patient advocate representative—What does the patient need to know and when?**

Panel Discussion: All speakers.

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- **One-day conference is designed to highlight PM progress and policy issues ;**

- **PCAST would precede and follow-up conference with in-depth study work to provide comprehensive review and final recommendations;**

- **Conference and study would strive to answer many of the following questions:**

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- **Research and Technology**
  - What is the current state of research in pharmacogenomics and pharmacogenetics (PGx)?
  - Are there estimates for annual/cumulative research expenditures for PM research?

  - What proportion of research is funded publicly and privately?
  - What are the current technological impediments to PGx research?
  - What is the relationship between sequencing the human genome and the progress of PM as it relates to research, data and equipment?
  - How do the tools for the human genome project and PGx/PM overlap (i.e. are the databases useful for PM, if not how do they differ, etc.)?

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■ **Research and Technology, continued**

➔ **How dependent is PM on information technology and where do the two overlap/connect?**

➔ **What is the state of IT research related to PM?**

➔ **What are the impediments to IT research related to PM?**

➔ **How would PM be integrated into a Personal Health Record or other electronic patient records for treatment, reimbursement, etc.?**

➔ **Are the IT issues for PM the same as for other medical applications (e.g. privacy) or do they differ? How so?**

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- ■ **Current Applications**
  - ➔ What are the current applications of PM and what is on the immediate (i.e. next 2-3 years) horizon?
  - ➔ How did these applications arise?
  - ➔ What technological and regulatory, or other, issues arose in their development?
  - ➔ How many of these issues have been resolved, corrected?
  - ➔ How well are these products working and accepted in practice today?
  - ➔ What types/how meaningful were the changes in pharma/diagnostic R&D, medical practice, reimbursement, etc. required to implement these products (i.e. Will PM require a "paradigm shift" in R&D, medical practice, regulation, IP)?

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- **Long Term Applications/Potential**
  - **What are the long term applications of PM?**
  - **Are there technological impediments to PGx/PM development/implementation?**
  - **How much funding has been provided for PM by the venture community and how many companies formed?**
  - **How broadly is PM practiced by traditional pharmaceutical companies and biotechnology companies?**
  - **At what different stages of pharmaceutical product development are PM tools applied and how are they used? (i.e. How much is PGx used as a tool today versus an end product and is that relationship expected to change in the future?)**

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- **Impact Upon Medical Practice**
  - How and where is PM impacting the practice of medicine today?
  - If PM proves to have broad and frequent medical applications, how will those change current practice, training and education for medical personnel?
  - What large practices/HMOs are participating in PM studies today? How and when do they expect to integrate PM into their practices?

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- **Impact Upon Payers**
  - How have payers dealt with reimbursement for approved/marketed PM products (diagnostic vs. therapeutic)?
  - What studies are payers currently conducting/participating in and how/when do they expect to integrate PM into reimbursement practices?
  - How is PM expected to change the nature and/or perceived value of diagnostic information versus therapeutic intervention and how would those changes impact the volume and/or frequency of individual testing, as well as treatment?
  - Have there been cost/benefit or other economic studies performed on PM products in the market today? How/when might such studies be performed? Who should participate?

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■ **Impact Upon Government/Legislation/Regulation**

  NIH, NSF, other research agencies
  - ➔ What level of funding is provided for PGx research and how does PM factor into different agency budgets/thinking?
  - ➔ Where does the Human Genome Project funding leave off and PGx/PM begin?
  - ➔ Are the private sector and federal research agencies interacting to facilitate PM research? If so, how?
  - ➔ Are there government-industry PGx/PM research collaborations and data/database sharing?

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■ **Impact Upon Government/Legislation/Regulation**

Privacy

➔ What are the privacy and ethical issues surrounding PM research and practice?

➔ Does current or pending legislation meet the needs of research and practice?

➔ What additional issues need to be addressed to facilitate/not impede progress in this field?

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- **Impact Upon Government/Legislation/Regulation**

  FDA
  - Has been active participant in PM, providing website, workshops, March 2005 guidance on "Pharmacogenomic Data Submissions" and more;
  - Do current policies and practices facilitate/obstruct bringing PM products to market? (Distinguish between diagnostic product regulation and therapeutic product regulation, as well as PGx data collected/used in clinical trials and combination products/filings.)
  - What was the experience for recently approved products?
  - Will further changes be necessary to provide approval for tests for existing/already approved therapies?
  - How will post-approval surveillance change for PM products?

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■ **Impact Upon Government/Legislation/Regulation**

CMS

➔ How has CMS dealt with reimbursement for approved/marketed PM products (diagnostic vs. therapeutic)?

➔ How is PM expected to change the nature and/or perceived value of diagnostic information versus therapeutic intervention and how would those changes impact the volume and/or frequency of individual testing, as well as treatment?

➔ Have there been cost/benefit or other economic studies performed on PM products in the market today? How/when might such studies be performed? Who should participate?

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■ **Impact Upon Government/Legislation/Regulation**

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➔ Are there specific intellectual property (IP) issues arising as a result of PGx/PM? How do these differ from other life sciences/medical IP issues? Should they be addressed differently/separately?

➔ Do PGx/PM research issues differ from product issues?

➔ Are there other industry models that might be useful to consider for the handling of PGx/PM intellectual property?

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CONCLUSION

- **Progress on Personal Health Record/Healthcare IT by federal agencies provides forum for discussion of downstream infrastructure applications such as PM;**

- **Preliminary interest by HHS and CMS to have PCAST provide private sector perspective on PM;**

- **Preliminary one-day PM conference proposed and outlined to highlight PCAST PM study;**

- **Propose 12 month study consistent with prior PCAST projects.**

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