

EXHIBIT

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Priorities for Personalized Medicine

Report of the
President's Council of Advisors on Science and Technology
September 2008



EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20502

September 15, 2008

President George W. Bush
The White House
Washington, D.C. 20502

Dear Mr. President:

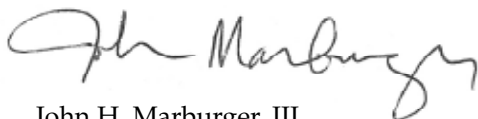
We are pleased to send you the report, *Priorities for Personalized Medicine*, prepared by your Council of Advisors on Science and Technology (PCAST). This report presents the scientific background of personalized medicine, its potential to improve health care and the obstacles standing in the way of its progress.

The Council believes that the convergence of scientific opportunity and public health need represented by personalized medicine warrants significant public and private sector action to realize the development of a promising class of new medical products. In conducting this extensive study PCAST examined eight major policy areas, engaging an extensive and diverse set of individuals and groups. PCAST ultimately identified three areas – technology and tools, regulation, and reimbursement – for its policy recommendations.

In order to develop technology and tools that will allow for the advancement of personalized medicine, PCAST recommends that the Federal government develop a strategic, long-term plan that coordinates public and private sector efforts to advance research and development relevant to personalized medicine. To stimulate and facilitate modernization of the regulatory process impacting personalized medicine, transparent, systematic, and iterative approaches should be utilized in the regulation of personalized medicine technologies and tools. PCAST also recommends that efforts to achieve cost-containment objectives for health care should not arbitrarily obstruct the adoption of innovative personalized medicine products. Finally, PCAST found that an office should be established within the Department of Health and Human Services to specifically coordinate their activities related to personalized medicine.

PCAST hopes that this report in its entirety helps lay a foundation for realizing important health care benefits from genomics-based molecular diagnostics, while providing a balanced assessment of the promise and current limitations of personalized medicine more broadly.

Sincerely,



John H. Marburger, III
Co-Chair



E. Floyd Kvamme
Co-Chair

September 15, 2008

The Honorable John H. Marburger, III
Director, Office of Science and Technology Policy
Executive Office of the President
Washington, DC 20502

Mr. E. Floyd Kvamme
Co-Chair, President's Council of Advisors on Science and Technology
Washington, DC 20502

Dear Jack and Floyd:

I am delighted to transmit to you PCAST's report, *Priorities for Personalized Medicine*, which was recently completed by our Subcommittee on Personalized Medicine.

PCAST commenced its study on personalized medicine in January 2007 with the ambitious goal of assessing eight major policy areas, including: technology / tools, regulation, reimbursement, information technology, intellectual property, privacy, physician and patient education, and economics. More than 110 individuals provided briefings to PCAST and its subcommittee at nine meetings and workshops, a series of phone calls and by written submissions. We were very pleased at the high level of interest in this subject as described by these individuals, who represented academic institutions, medical diagnostic, direct to consumer, service and imaging companies, biotechnology and related tools companies, pharmaceutical and information technology companies, insurance companies and providers, patient advocates, venture capital firms, trade and professional associations and government agencies.

I presented our preliminary recommendations at the April 2008 PCAST Meeting, where we all noted the assortment of Federal agencies with involvement in and/or oversight of emerging personalized medicine products and services. As important, we also recognized the broad range of levels at which policy recommendations might be directed in our communication with the President. These observations and experiences are not uncommon for health care and we were not spared the dilemma of how best to prioritize our study conclusions. As a result, the subcommittee narrowed the focus of the report into areas we considered the most pressing and timely: technology / tools, regulation and reimbursement. We also feel the U.S. Department of Health & Human Services (HHS) could be most effective in assuring progress for continued innovation in this field through a more formalized coordination office.

It is important to point out that we did not choose to detail in our report policy recommendations in five areas we studied, which still remain key components to the long term development and success of personalized medicine. Our reasons for this decision relate to the timing of progress and work in each, involving: significant ongoing government activity (information technology and privacy), the early stage of personalized medicine product development (physician and patient education and economics) and the need for more comprehensive policy recommendations extending beyond the scope of our study of personalized medicine (intellectual property and privacy). With particular respect to intellectual property, discussion of Congressional attempts at patent reform has been underway for several years and certain policy issues dominate the current, critical dialogue in this area – with differing views from a range of key industries. We encourage a separate, future PCAST subcommittee to examine the outstanding intellectual property issues across all domains and prepare a report addressing these issues.

Several observations have served to peak our attention in the course of this study on personalized medicine. First, we have been impressed with the efforts of Secretary Leavitt and his staff in supporting

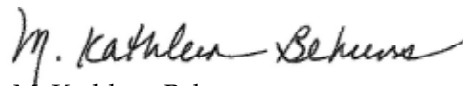
advancements in this field throughout different agencies in HHS. The Secretary's leadership has accelerated the rate at which such technological developments historically permeate policy discussions and decisions – though there is also understandable concern this progress might slow or end with an upcoming change in administration.

Second, first generation personalized medicine products are giving us a vision of even broader possible applications. Not only do they have the potential to expedite drug testing and approval, which has slowed significantly in this decade (in a backdrop of increasing development expense), they promise to improve the quality of patient care.

Finally, there is also widespread appreciation that, if we begin to address the quality and delivery of patient care, we might eventually harness rising health care costs. The rapidly increasing number of enrollees in the Federal Medicare insurance program will keep the health care debate focused on costs for many years to come. While there are many aspects of personalized medicine that require significant additional study, this field is developing specialized tools and accelerating the use of others that offer the means to answer many questions in this debate.

I feel the President's support of, and the long standing efforts by Secretary Leavitt in facilitating the development of, personalized medicine have contributed greatly to early progress in this field. At the same time, I hope this study contributes a broader understanding and recognition of the future opportunities that may arise from personalized medicine – but ones that will only emerge with a continuation of current favorable policies in this area.

Sincerely,

A handwritten signature in cursive script that reads "M. Kathleen Behrens".

M. Kathleen Behrens

Chair

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Executive Summary

“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

The principle of adjusting treatment to specific patient characteristics has, of course, always been the goal of physicians. However, recent rapid advances in genomics and molecular biology are beginning to reveal a large number of possible new, genome-related, molecular markers for the presence of disease, susceptibility to disease, or differential response to treatment. Such markers can serve as the basis of new genomics-based diagnostic tests for identifying and/or confirming disease, assessing an individual’s risk of disease, identifying patients who will benefit from particular interventions, or tailoring dosing regimens to individual variations in metabolic response. These new diagnostics can also pave the way for development of new therapeutics specifically targeted at the physiological consequences of the genetic defect(s) associated with a patient’s disease.

The current high level of interest in personalized medicine from a policy perspective is attributable not only to the promise of improved patient care and disease prevention, but also to the potential for personalized medicine to positively impact two other important trends – the increasing cost of health care and the decreasing rate of new medical product development. The ability to distinguish in advance those patients who will benefit from a given treatment and those who are likely to suffer important adverse effects could result in meaningful cost savings for the overall health care system. Moreover, the ability to stratify patients by disease susceptibility or likely response to treatment could also reduce the size, duration, and cost of clinical trials, thus facilitating the development of new treatments, diagnostics, and prevention strategies.

The President’s Council of Advisors on Science and Technology (PCAST) believes that the convergence of scientific and clinical opportunity and public health need represented by personalized medicine warrants significant public and private sector action to facilitate the development and introduction into clinical practice of this promising class of new medical products. In developing recommendations for such action, PCAST considered eight major policy areas – technology/tools, regulation, reimbursement, information technology, intellectual property, privacy, physician and patient education, and economics. To understand the impact of these policy areas on the development of personalized medicine, PCAST solicited input from a broad range of stakeholders representing academic institutions, medical diagnostics and imaging companies, biotechnology and pharmaceutical companies, insurance companies, patient providers and advocates, venture capital firms, trade and professional associations, and government agencies.

Based on these deliberations, PCAST determined that specific policy actions in the realm of genomics-based molecular diagnostics had the greatest potential to accelerate progress in personalized medicine. This does not mean that PCAST discounts the importance of parallel developments in genomics-linked therapeutics; rather, PCAST has concluded that, at present, the pace of change is most rapid, and the policy hurdles are greatest, in the realm of diagnostics.

With regard to genomics-based molecular diagnostics, PCAST further identified three areas – technology/tools, regulation, and reimbursement –for its policy recommendations. This prioritization reflects the critical importance of defined policy actions in each of these areas to near-term progress in the development and introduction of these important health care innovations. Accordingly, PCAST has focused its recommendations on these areas. The other policy areas, while still very important over the long term to the success of new genomics-based molecular diagnostics, were deemed less urgent within the context of the present report because of significant ongoing government activity (information technology and privacy), the early stage of personalized medicine product development (physician and patient education and economics) or the need for more comprehensive policy recommendations extending beyond the scope of personalized medicine (intellectual property and privacy). With particular respect to intellectual property, PCAST strongly recommends the convening of a separate PCAST

subcommittee to examine the outstanding intellectual property issues across all domains and prepare a report addressing these issues. Finally, because the three policy areas on which PCAST is focusing its recommendations are under the purview of the Department of Health and Human Services (HHS), PCAST concluded that HHS should establish a Personalized Medicine Coordination Office.

This report presents the scientific and clinical background of personalized medicine, its potential to improve health care, and the obstacles standing in the way of its progress. It reviews the landscape of personalized medicine by describing the diagnostic tools involved, the clinical domains affected, and the requirements for implementation in clinical practice. The report also explains the rationale for focusing on the three priority areas of technology/tools, regulation, and reimbursement and provides a brief review of the issues facing the remaining five policy areas. The report discusses in detail the technical background, policy issues, and challenges affecting each of the three priority areas and provides specific recommendations for each area.

Challenges and Policy Recommendations

Priority Area 1: Technology and Tools

Challenges

Despite the promise of genomics-based molecular diagnostics to advance personalized medicine, significant challenges remain in validating the genomic/clinical correlations required to advance these products into clinical use. While an increasing number of candidate genetic markers are being discovered, clinical validation of these markers has proceeded at a slow pace. To correct this imbalance between discovery and validation, public and private sector research will need to be coordinated and prioritized more effectively, and the tools required for validation studies will need to be strengthened.

Public/private sector coordination is necessary because the validation of genetic correlations with disease – the key element of translational research in this area – shares many of the attributes of the “development” side of research and development (R&D). Historically, development has been the purview of industry rather than of government-supported academic science, which has instead focused on discovery research. However, because the validation of genomic correlations with disease is a new, expensive, and high risk R&D area, industry may not be willing to make a substantial investment until a clearer path to validation is developed through the use of public funds. Therefore, in order to move genomic discoveries to practical application, public investment in the translational research necessary to validate genomic/clinical correlations must be increased and also coordinated with industry investment.

Clinical and population studies to validate genomic correlations with disease and disease outcomes will also require significant investment in the development of three key translational research tools. The first tool includes collections of high quality biological specimens accompanied by comprehensive disease annotation. The second tool encompasses study designs addressing biomarker standardization and incorporating the sophisticated statistical methods necessary for demonstrating the clinical validity and utility of genomic profiles. The third tool represents large population cohorts for longitudinal health and disease studies. Without the development of these tools, personalized medicine is unlikely to advance beyond the stage of promising discoveries.

Policy Recommendations

1. The Federal government should develop a strategic, long-term plan that coordinates public and private sector efforts to advance research and development relevant to personalized medicine.

- The Federal government, through the leadership of HHS, should join with the private sector to create a public/private sector “Personalized Medicine R&D Roadmap” for coordinating discovery and translational research in personalized medicine.
- The National Institutes of Health (NIH) and other agencies such as the Departments of Energy and Defense should evaluate the proper balance of government funding for discovery versus translational research relevant to personalized medicine.

- Under HHS leadership, NIH should develop a coordinated process to identify and prioritize diseases and common therapies that would benefit from the application of genomics-based molecular diagnostics.
- 2. The Federal government should make critical investments in the enabling tools and resources essential to moving beyond genomic discoveries to personalized medicine products and services of patient and public benefit.**
- NIH should lead, stimulate, and coordinate public and private sector efforts to develop an integrated nationwide network of standardized biospecimen repositories to support research in personalized medicine.
 - NIH should develop a funding program for academic/industry collaborative projects addressing biomarker standardization, statistical methods, and other aspects of study design necessary for validating the clinical utility of molecular diagnostics based on genomic correlations with disease characteristics.
 - NIH should develop a large population cohort for investigating genetic and environmental health impacts by enrolling and following over time a large, representative sample of the U.S. population.

Priority Area 2: Regulation

Challenges

The Food and Drug Administration (FDA) has made considerable progress in defining its approach to the regulation of genomics-based molecular diagnostics. Nevertheless, FDA guidance remains ambiguous or incomplete in several important areas, including:

- Criteria that define risk for products, including diagnostic tests, where information is the key result
- Standards for study design and product performance with regard to regulatory review of new diagnostic products
- Coordination of potentially redundant requirements between FDA and the Centers for Medicare and Medicaid Services (CMS), operating under the authority of the Clinical Laboratory Improvement Amendments legislation
- Regulatory approach to co-development of diagnostics and therapeutics
- Criteria and procedures for adjusting therapeutic product labeling to incorporate use of diagnostics
- Regulatory approach to information technology-based clinical decision support systems

Progress to date on the Critical Path Initiative launched by FDA in 2004, which was intended to stimulate and facilitate modernization of the development path for drugs and devices, has been slow in part because of inadequate funding. Furthermore, the private sector's interaction with the FDA with regard to regulatory policy needs to be more proactive and constructive.

Policy Recommendations

3. FDA should implement a more transparent, systematic, and iterative approach to the regulation of genomics-based molecular diagnostics.

- In its final guidance on *in vitro* diagnostic multivariate index assay (IVDMIA) tests, FDA should clarify its definition of risk in light of the intended IVDMIA use, provide illustrative examples distinguishing products that will be subject to full premarket approval review from those that will not, and provide adequate transition time for any new requirements.
- FDA and CMS should identify potential overlap and redundancy in their oversight of laboratory-developed tests, eliminate redundant requirements, and issue guidance to clarify the relationship between their respective requirements.

- FDA should finalize its draft concept paper on drug-diagnostic co-development and provide clarity with regard to requirements and standards.
- FDA should clarify the criteria and procedures for determining when labeling of a therapeutic product will incorporate information on related diagnostic tests, as well as establish the circumstances under which such tests will be either recommended or required.
- FDA should issue guidance concerning the regulation of automated clinical decision support systems.
- FDA should enhance communication with affected constituencies by issuing more frequent and timely Requests for Information and draft guidance.

4. The FDA Critical Path Initiative should be adequately funded to support its envisioned research efforts that are critical to the progress of personalized medicine.

- Priority projects should include the use of biomarkers to facilitate product development and regulatory review and the development of standards for clinical trial design and biostatistical analysis for validation of genomics-based molecular diagnostics.
- Congress should fund the Reagan-Udall Foundation and its board membership should be expanded to include representatives from the venture capital community and small companies involved in genomics-based diagnostic development.

5. Industry should adopt a proactive and constructive role as FDA seeks to identify and fulfill its regulatory responsibilities related to personalized medicine.

- Industry should respond in a substantive and positive way to Requests for Information and draft guidance documents, including submission of alternative approaches, and inform FDA of emerging issues that require policy development.
- Test developers should take advantage of existing FDA procedures for advance consultation to achieve a timely and shared understanding of the hurdles to regulatory approval.
- Industry should provide FDA with annual projections of the number and type of products in the development pipeline based on emerging or rapidly evolving technologies.
- Industry should convene meetings of trade and professional associations to anticipate regulatory issues that are likely to arise with new technological developments and provide FDA timely alerts concerning such emerging issues.

Priority Area 3: Reimbursement

Challenges

There are three key challenges to achieving cost-containment objectives for health care without arbitrarily obstructing the adoption of innovative genomics-based molecular diagnostics. The first challenge is that reimbursement of genomics-based molecular diagnostic tests as low-margin commodity items – as is common practice for laboratory diagnostics – will reduce the likelihood that such products will be developed by industry. The second challenge is the need to develop standards for the evidence that CMS and other payors will require to validate the benefits of these tests in real-world settings. The third challenge involves the procedural hurdles associated with coding systems, bundled payment systems, and complex billing procedures and requirements that can especially impact reimbursement for innovative molecular diagnostics.

Policy Recommendation

- 6. Public and private payors should determine coverage policies and payment rates for genomics-based molecular diagnostics in light of their overall impact on patient care, as demonstrated by evidence from clinical trials and other well-designed empirical studies.**
 - Public and private payors should reimburse for genomics-based molecular diagnostics commensurate with the clinical benefits provided and should collaborate with test developers to establish new, more flexible coding approaches for reimbursement.
 - Public and private payors should collaborate to expand “coverage with evidence development” programs that extend coverage and reimbursement while a product is being investigated for appropriate use and effectiveness.
 - Public and private payors should collaborate in the development of standards for clinical trial designs that would be accepted as providing evidence sufficient for coverage decisions.

HHS Coordination Challenges

As the three priority areas on which PCAST is focusing its recommendations come under the purview of HHS, more systematic coordination of activity across HHS is necessary to make the most effective use of limited resources.

Policy Recommendation

- 7. HHS should establish a Personalized Medicine Coordination Office within the Office of the Secretary of HHS to coordinate all activities relevant to personalized medicine.**
 - The coordination office should be charged with coordination of all HHS activities relative to personalized medicine in order to facilitate progress while ensuring that personalized medicine products meet the highest standards of safety, efficacy, and clinical utility.
 - The coordination office should be responsible for monitoring the progress of personalized medicine and, as new innovations or challenges develop, for ensuring that all HHS agencies work together to address emerging needs.

I. Introduction

“Personalized medicine” refers to the tailoring of medical treatment to the specific characteristics of each patient. In an operational sense, however, personalized medicine does not literally mean the creation of drugs or medical devices that are unique to a patient.¹ Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

The principle of adjusting treatment to the specific characteristics of the patient is not new; it has always been the goal of physicians. However, rapid advances in genomics and molecular biology, including most prominently the sequencing of the human genome, promise to vastly increase physicians’ ability to stratify patients in clinically useful ways. A key product of these scientific advances has been the identification of an array of possible new genome-related molecular markers for disease susceptibility or for specific variants of disease that are especially responsive to particular treatments. These markers can include the presence or expression² of particular gene variants, patterns of gene variants or their expression, specific proteins, or variant forms of proteins. Such markers can form the basis of new genomics-based diagnostic tests for assessing individuals’ risk of disease, identifying patients who will benefit from particular interventions, or tailoring medication doses to accommodate individual variation in metabolic response.³

In addition to genomics-based diagnostics, another key component of personalized medicine is the expanding group of targeted therapies designed to counteract the specific physiologic mechanisms by which genetic alterations lead to particular forms of disease. Because these therapies are targeted at the consequences of defects in single genes, they are most useful in cases where a single genetic defect defines the disease (e.g., Factor VIII in hemophilia and bcr-abl – targeted by the drug Gleevec® [imatinib mesylate] – in chronic myeloid leukemia). Historically, such therapies have been developed using classical genetic or physiologic characterization and not the recent advances in genomic technologies. However, as genomic technologies identify new markers of disease, new targeted therapies can be developed that are specifically linked to the use of a genomics-based diagnostic test for identifying appropriate patients.

These scientific advances have occurred against the backdrop of two important trends in U.S. health care that have focused intense interest on the promise of personalized medicine.

The first trend is the ever-increasing cost of health care. As the “baby boom” generation approaches retirement age and increases its demands on the health care system, any respite from cost pressures seems remote. While many health care cost reduction strategies will require difficult choices concerning access to or quality of care, personalized medicine – the use of improved diagnostic tests to better match patients to treatments – seems to offer the prospect of combining improved patient outcomes with reduced costs.

¹ There are exceptions to this rule in the area of immunotherapy, for example, patient-specific cancer vaccines that are created using the patient’s own tumor cells or autologous stem cell transplants.

² Gene expression refers to the process by which cells convert genetic information contained in DNA into the proteins that are responsible for the structure and function of all living cells and tissues.

³ Over the years, many diagnostic tests have become available to detect the genetic abnormalities associated with a wide range of rare inherited disorders. The GeneTests Web site (<http://www.genetests.org/>, accessed July 17, 2008), funded by the National Library of Medicine and the National Human Genome Research Institute, provides a comprehensive, annotated database of such tests. The new technologies, however, promise to extend the power of genomic analysis to a broader range of more common and/or late-onset diseases with wider public health impact.

The scope for such savings may be broad. Physicians have long observed substantial variation in patient response to treatments for different cancers as well as for such common conditions as hypertension, heart failure, depression, high cholesterol, and asthma. Finding the best medication for a given patient often involves trial and error; sometimes a physician may exhaust all possibilities without finding an option that is effective. The ability to distinguish in advance those patients who will benefit from those who will incur cost and suffer side effects without gaining benefit could both reduce costs and improve quality of care.

The second trend relates to the development of new treatments. The rate at which new drugs and devices are submitted to the Food and Drug Administration (FDA) and approved for marketing has not kept pace with the accelerating progress in biomedical discovery research. This is due in part to the continually increasing cost, complexity, and duration of the research and development (R&D) needed to bring a new product to market,⁴ a trend that is likely to be exacerbated by increased attention to safety in the wake of the Vioxx® episode.⁵ Mindful of the enormous public investment in biomedical research, many patient advocacy groups are demanding increased attention to clinical impacts and patient benefit.⁶ Within the scientific community, there is growing awareness that “the enormous resources being put into biomedical research, and the huge strides made in understanding disease mechanisms, are not resulting in commensurate gains in new treatments, diagnostics and prevention.”⁷

The core capability of personalized medicine – the ability to stratify patients by disease susceptibility or likely response to treatment – can also be applied in the design of clinical trials to reduce their size, duration, and cost. In some cases, new knowledge about factors influencing patient response can even “rescue” drugs that benefit specific populations but whose effects are lost in the statistical noise when the drugs are tested in unselected populations dominated by nonresponders. Thus, personalized medicine may also be part of the solution to the “pipeline” problem for drugs and medical devices.

This compelling convergence of public health need and scientific opportunity has raised personalized medicine to the top of the public policy agenda. Under the leadership of Secretary Michael Leavitt, the Department of Health and Human Services (HHS) has identified personalized medicine as a priority and supported a wide range of initiatives to stimulate progress in the field.⁸ The Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) has recently released two major reports addressing key aspects of personalized medicine.⁹ The Institute of Medicine has created a Roundtable on Translating Genomic-Based Research for Health¹⁰ which recently released a summary report from its December 4, 2007, Workshop on the Diffusion and Use of Genomic Innovations in Health and Medicine.¹¹ The Personalized Medicine Coalition has been organized as an independent, not-for-profit, cross-sector education and advocacy group.¹² Conferences on personalized medicine sponsored by academic research centers, investment firms, and others have proliferated as researchers and policymakers in government, academia, and industry seek to understand the implications of genomic science for health care.

⁴ *The Pursuit of High Performance through Research and Development: Understanding Pharmaceutical Research and Development Cost Drivers*, prepared by Accenture for the Pharmaceutical Research and Manufacturers of America, 2007; accessed June 24, 2008 at <http://www.phrma.org/files/Accenture%20R&D%20Report-2007.pdf>.

⁵ See Vioxx® (rofecoxib) Information Center, <http://www.merck.com/newsroom/vioxx/> and Vioxx (rofecoxib) Questions and Answers, <http://www.fda.gov/CDER/DRUG/infopage/vioxx/vioxxQA.htm>, both accessed August 9, 2008.

⁶ See, for example, the overview and mission statement for the organization *FasterCures*, accessed June 24, 2008 at <http://www.fastercures.org/about/>.

⁷ Butler D, “Crossing the Valley of Death,” *Nature* 2008 Jun 12;453(7197):840-2.

⁸ <http://www.hhs.gov/myhealthcare/>, accessed June 24, 2008.

⁹ *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, Report of the Secretary’s Advisory Committee on Genetics, Health, and Society, April 2008, accessed June 24, 2008 at http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf; *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges*, Report of the Secretary’s Advisory Committee on Genetics, Health, and Society, May 2008, accessed June 24, 2008 at http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_Report.pdf.

¹⁰ <http://www.iom.edu/CMS/3740/44443.aspx>, accessed June 24, 2008.

¹¹ http://www.nap.edu/catalog.php?record_id=12148, accessed June 24, 2008.

¹² <http://www.personalizedmedicinecoalition.org/>, accessed June 24, 2008.

Appendix B lists several applications of genomics-based diagnostics (often with linked therapeutics) that have reached the market, establishing proof of concept. At the very least, many more such advances that benefit specific groups of patients can be expected. More optimistic observers envision a future in which the strategy of genomics-tailored treatment is so powerful and broadly useful that it fundamentally transforms clinical practice, leading to a new, qualitatively different, more cost-effective era of truly personalized medicine. Whether such a vision is realistic remains to be seen. But even under the most conservative scenarios for progress in personalized medicine, the benefit in improved health and reduction in human suffering will be great.

However, realization of the benefits of personalized medicine is threatened by an array of obstacles. These obstacles include:

- Methodological and logistical challenges in validating apparent correlations between genetic markers and disease, which are being generated at an accelerating rate through the latest genomic technologies
- Regulatory and reimbursement systems that were not designed to accommodate complex genomics-based diagnostics that have the power to sway high-stakes medical decisions
- Absence of the electronic medical record-linked decision support tools needed to effectively integrate the results of genomics-based diagnostic tests into routine clinical practice
- Intellectual property laws and practices that may present barriers to investment in genomics-based diagnostics
- Privacy concerns that may limit patient acceptance of genomics-based diagnostics
- Education of patients and physicians on the proper use and limitations of new genomics-based diagnostics

The purpose of this report is to present the recommendations of The President's Council of Advisors on Science and Technology (PCAST) for overcoming these obstacles. This report differs from the many other recent reports on personalized medicine in two important ways. The first relates to PCAST's distinctive role, which is to advise the President concerning the private sector's perspective on key science and technology issues. In analyzing personalized medicine, PCAST has taken a comprehensive view of the innovation ecosystem, and makes recommendations for both government and private action. Second, rather than issue a lengthy list of recommendations addressing every facet of personalized medicine, PCAST has chosen to identify areas that it considers the most important obstacles to progress today, and to focus a limited number of recommendations on these priority areas.

To provide context and make the discussion more concrete, Section II briefly outlines the range of personalized medicine products and tools that are beginning to impact clinical practice today or are likely to do so in the foreseeable future, and summarizes the likely clinical focus of personalized medicine in the near term. Section III describes the process through which PCAST assessed the status of personalized medicine and the relative importance of the obstacles to its progress, while Section IV delineates the subset of these obstacles that PCAST has identified as priorities for immediate action. The remaining sections (Sections V-VIII) explain in detail each of these prioritized issues and present PCAST's recommendations.

II. Landscape of Personalized Medicine

Introduction

The goal of personalized medicine is to reduce the burden of disease by targeting prevention or treatment more effectively. Its strategy is to sort patients into narrower diagnostic categories that correlate more strongly with the efficacy of specific therapies or preventive measures. Its key enabling technologies are advances in genomics and molecular biology that offer the potential to radically improve our ability to characterize susceptibility to disease and to treatment effects.

Diagnostic Tools

The vision of clinical practice transformed by personalized medicine encompasses a wide range of diagnostic tools. Some address diagnosis *per se*, some are used to guide treatment, and some identify the need for prevention. Most are aimed at physicians, but some may be marketed directly to consumers. Several products are on the market today (see Appendix B) and many more are in the development pipeline, while new concepts ripe for development are continually emerging from discovery research.

Molecular Diagnostics

In vitro molecular diagnostics are laboratory tests that can be used on blood, tissue, or other biological samples to identify the presence of specific molecular biomarkers. Today, much attention is focused on genes and their protein products as biomarkers. These may be assessed by measuring either the presence of a gene or protein variant or its level of expression or activity. However, other products of human physiology including lipids, carbohydrates, and other metabolic intermediates and end-products can also serve as biomarkers.

Molecular diagnostics can be used in a variety of ways to inform personalized medicine:

- **Assess the likely efficacy of specific therapeutic agents in specific patients.** An example is the use of the Oncotype DX[®] test in patients with newly diagnosed, early stage invasive breast cancer to quantify the risk of systemic recurrence and assess the value of chemotherapy.¹³
- **Identify patients who may suffer disproportionately severe adverse effects from a given treatment or dosage.** One example is tests for genetic variation in the activity of an enzyme called thiopurine methyltransferase (TPMT), which affects the level of bone marrow toxicity experienced by patients receiving purine drugs for acute lymphocytic leukemia, renal transplant rejection, and severe active rheumatoid arthritis.¹⁴ Another example is a test to detect a gene variant that elevates the risk for white blood cell depletion from Camptosar[®] (irinotecan), an agent used in the treatment of colorectal cancer.¹⁵ Notably, as this report was being completed, FDA issued an alert and announced forthcoming changes in labeling for the anti-HIV agent abacavir. Patients with the HLA-B*5701 allele who take abacavir are at significantly higher risk for serious and sometimes fatal hypersensitivity reactions; this allele can be detected by genetic tests already on the market.¹⁶ The ability to identify patients who are likely to suffer disproportionate adverse effects may also be of value in designing clinical trials to “rescue” agents which have failed due to toxicity. Several examples of this category of molecular diagnostic are already on the market (see Appendix B).

¹³ <http://www.genomichealth.com/oncotype/>, accessed April 24, 2008.

¹⁴ AZASAN prescribing information, http://www.salix.com/assets/pdf/prescribe_info/azasanpi.pdf, accessed April 24, 2008.

¹⁵ <http://www.twt.com/clinical/ivd/ugt1a1.html>, accessed May 21, 2008.

¹⁶ Information for Healthcare Professionals – Abacavir (marketed as Ziagen) and Abacavir-containing medications, <http://www.fda.gov/cder/drug/InfoSheets/HCP/abacavirHCP.htm>, accessed August 9, 2008.

- **Determine optimal dosages for drugs whose therapeutic effect is known to vary widely.** For example, warfarin anticoagulation therapy is routinely dosed through trial and error. A number of tests for genetic markers that correlate with warfarin metabolism and are believed to be important in patient dosing are already on the market, and additional markers are under investigation.
- **Assess the extent or progression of disease.** Molecular diagnostics have the potential to provide more accurate and timely information on disease prognosis or treatment effectiveness than the imaging and pathology methods currently used for this purpose, though future diagnostic approaches may integrate all of these methods.
- **Examine surrogate measures for clinical outcomes.** Researchers are investigating whether biomarker-based molecular diagnostics can provide reliable proxies for longterm outcomes such as relapse or survival. Such tests could be used to shorten the length and expense of clinical trials.
- **Identify patients who can benefit from specific preventive measures.** To have a meaningful clinical impact, such diagnostics would have to identify individuals who have a substantially elevated risk of a specific condition for which a well-defined intervention is available that is affordable and tolerable within the patient's lifestyle. Products or services in this category may be marketed directly to consumers, as well as to health care providers.

Personal Genomes and Genetic Profiles

Rapid advances in the technology and reduction in the cost of DNA sequencing are likely to make complete personal genomic sequences widely available at an affordable cost, perhaps even within the next decade. In fact, whole-genome sequencing has recently become commercially available, albeit at a price – \$350,000 – that all but a handful of consumers will find prohibitive.¹⁷

However, speculation about the potential impact of the low-cost “\$1,000 genome” often overlooks two critical points. First, human illness is a consequence not solely of genetic inheritance, but also of its interaction with environment and behavior. Second, the limiting factor in clinical application of genomic information will be not the availability of patients' genomes, but rather the lack of robust, clinically validated correlations between genomic markers or profiles and specific clinical phenomena such as susceptibility to disease or to the effects of a particular treatment. Visions of the personal genome as a uniquely powerful diagnostic tool or as a substitute for many existing diagnostic and risk assessment techniques are premature.

In addition to whole-genome sequencing, a number of companies have begun to utilize large numbers of known markers to offer genetic profiles directly to consumers.¹⁸ As with personal genomes, the predictive value and clinical utility of these genetic profiles is unproven and remains the focus of considerable skepticism and controversy. Direct-to-consumer marketing of such profiles, or of well-validated markers for specific inherited disorders, raises significant scientific, legal, and ethical issues that are both complex and beyond the scope of this report.

Linked Diagnostics and Therapeutics

Genomics-based diagnostics also have the potential to lead to development of new drugs or biologic agents that are targeted to the genetic or physiologic defect identified by the diagnostic. The best known example is already on the market: the use of HER2 tests to guide use of the drug Herceptin® (trastuzumab) by identifying those breast cancer patients whose tumors over-express the HER2 gene.¹⁹ Such linkages may be established via coordinated development of the agent and the test, through development of a relevant test after an agent has reached the market, or (in principle, but rarely in current practice) through the development of a new agent for which an already-marketed diagnostic can serve as a differentiator.

¹⁷ <http://www.knome.com/Recent%20News/tabid/58420/Default.aspx>, accessed April 24, 2008.

¹⁸ See, for example, 23andMe (<http://www.23andme.com/>) and Navigenics (<http://www.navigenics.com/>). Both accessed April 24, 2008.

¹⁹ <http://www.herceptin.com/herceptin/professional/testing/important.jsp>, accessed April 24th, 2008.

By identifying patients who are most likely to benefit from a therapeutic agent, linked diagnostics may offer the collateral benefit of enabling the design of smaller, faster, and less expensive clinical trials for those agents with a higher likelihood of success. The development of new linked diagnostics may also make it possible to “rescue” agents that have shown little apparent efficacy in large trials of unselected patient populations.

Clinical Domains

Today, most applications of innovative genomics-based diagnostics are utilized for cancer. Research on the genetic mutations that lead to loss of normal growth control in tumor cells has identified a range of targets that may be accessible to pharmacologic intervention, and whose presence can be detected using molecular assays for the presence or expression of a variant gene or its protein product. Because of the life-or-death nature of cancer treatment decisions and the high cost of cancer care, the use of relatively expensive tests can often be justified.

High-stakes, high-cost conditions in other clinical domains are also likely candidates for commercialization of innovative molecular diagnostics in the near term. Two examples already on the market are the AlloMap® molecular expression test,²⁰ which provides noninvasive monitoring of patient risk for acute cellular rejection following cardiac transplantation, and the Trofile™ HIV tropism assay,²¹ which is used to identify patients who may benefit from the novel anti-HIV drug Selzentry™ (maraviroc).

Common conditions managed in primary care practice are often influenced by multiple genes, in ways that are not yet well understood. The rapidly-evolving field of warfarin pharmacogenomics exemplifies some of the challenges that will be faced in implementing personalized medicine for such conditions.²² There is strong evidence that the extensive variation in warfarin metabolism can be explained largely by a mix of genetic and clinical factors, so that in principle an algorithm based on these factors should be able to help clinicians arrive at optimal dosing sooner and with a reduced risk of bleeding incidents.

Several tests are already on the market that allow assessment of some, but not all, of the genetics-related risks associated with warfarin dosing. However, physicians generally remain reluctant to use them for several reasons. Robust algorithms for translating genomic test results into initial and/or subsequent dosing are not widely available and will likely change as additional genetic factors are identified and the relative contributions of each are determined. In many practice settings, lengthy turnaround times mean that test results are unavailable for timely initiation of therapy. Patients who have their initial dosage adjusted in light of such tests still require ongoing monitoring to assure that bleeding time remains within an acceptable range, so there is little or no net reduction in physician burden. Finally, as yet there is no firm evidence that optimizing initial dosage will ultimately reduce bleeding events, and thus it is not yet known whether any important clinical benefit will be gained.

Despite a promising theoretical case for the benefits of pharmacogenomics-based patient management, realization of these benefits in practice for common conditions affected by multiple genes will be a complex process that will depend on substantial investment in clinical research well beyond the initial demonstration of gene-disease correlations. For such conditions, widespread adoption of pharmacogenomic diagnostics is likely to be some years away.

Clinical Decision Support

To date, few genomics-based diagnostic tests have reached the market, and these few products have been targeted primarily at clinical specialists and subspecialists who have been able to assimilate them into practice without special measures. However, if the number of innovative personalized medicine diagnostics and linked diagnostic-therapeutic combinations reaching the market increases substantially, widespread adoption of these products and

²⁰ <http://www.allomap.com>, accessed April 24, 2008.

²¹ <http://www.trofileassay.com>, accessed April 24, 2008.

²² Check W, “Too fast or too slow on PGx testing?” CAP Today Feature Story, March 2008, College of American Pathologists, http://www.cap.org/apps/portlets/contentViewer/show.do?printFriendly=true&contentReference=cap_today%2Fcover_stories%2F0308_TooFastOrSlow.html, accessed April 24, 2008.

services – especially in general practice settings – may depend on the availability of IT-based clinical decision support systems that are integrated with electronic medical records and can be accessed as part of routine practice workflows. Such systems draw on the information present in the medical record to give the physician patient- and situation-specific information on the diagnostics and therapeutics relevant to the patient’s care.

Medical Technology Innovation Pathway

Genomics-based diagnostics, as well as therapeutics targeted at the physiologic consequences of genetic variation in disease, must traverse a complex pathway to move from a fundamental discovery in basic biomedical science to a product or service that is available in routine clinical practice. These steps are presented in simplified and idealized form in the Medical Technology Innovation Pathway, shown in Figure 1.

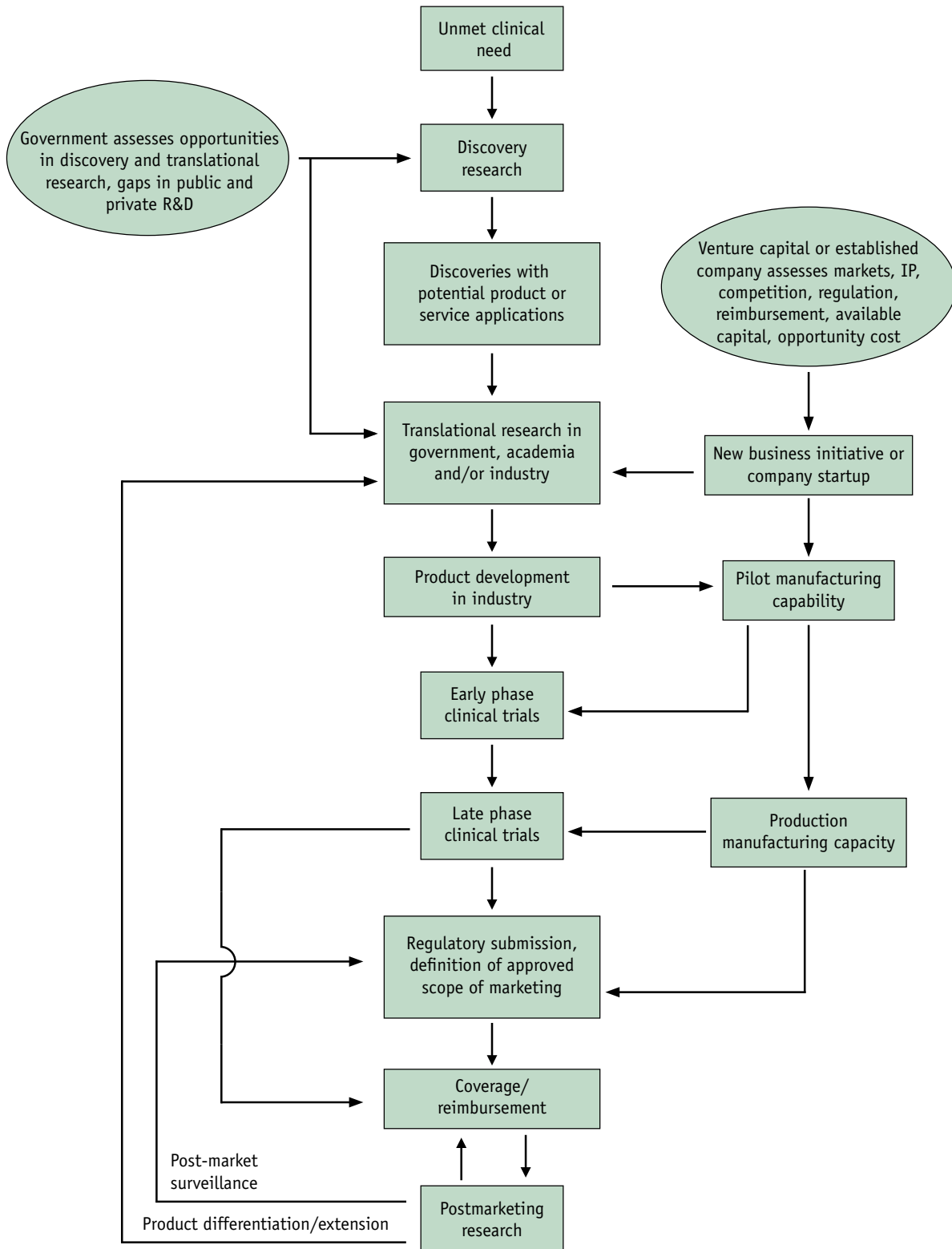
Although the pathway is a simplified representation, it helps to clarify key features of the innovation process that are central to understanding the policy issues addressed in this report. These features include:

- The complex interactions between government, academia, and industry that are required to bring a new biomedical technology to fruition
- The continual assessment of needs, opportunities, and the opportunity cost of alternative investments conducted by government and industry as they evaluate how to spend scarce resources most productively
- The role of government funded discovery and translational research in continually reseeding the development pathway with essential technologies and tools
- The challenging, nonroutine nature of the “development” phase of the R&D process for medical products
- The important hurdles to market access for new products or services posed by regulatory and coverage/reimbursement processes
- The provisional nature of market access, as the regulatory and reimbursement status of marketed products may be subject to revision in light of ongoing surveillance and research

As is reflected in the pathway diagram, private sector investment decisions take into account scientific and technological considerations, along with market conditions and intellectual property, regulatory, and reimbursement hurdles that are expected to apply to a given product. This assessment considers not only those factors that are narrowly relevant to a particular product, but also overall trends in intellectual property, regulatory, and reimbursement policy that are relevant to a biomedical product class, such as genomics-based molecular diagnostics. Intellectual property, regulatory, or reimbursement policies can be barriers to investment not only when they raise well-defined hurdles to product development, but also in situations where a lack of clear policy or clear communication of intended policy changes raises substantial concern that new hurdles will be imposed. Because all of these factors are considered at the outset, an unfavorable assessment of the investment climate for a product – or, indeed, for an entire class of products – can mean that no investment in that product or class will be forthcoming at all.

Figure 1. Medical Technology Innovation Pathway

Medical Technology Innovation Pathway



III. PCAST Deliberations

PCAST initiated its study in January 2007, having identified eight major policy areas to consider and evaluate:

- Technology/Tools
- Regulation
- Reimbursement
- Information Technology
- Intellectual Property
- Privacy
- Physician and Patient Education
- Economics

Numerous public presentations, private subcommittee meetings and workshops, and telephone interviews were conducted to learn the views of a broad range of stakeholders and provide subject matter expertise to PCAST on these eight topics. More than 110 individuals provided briefings, interviews, or presentations. The following major events were held involving the participants, as listed in Appendix A:

- Public presentations at PCAST meetings on January 9, 2007; April 24, 2007; September 11, 2007; and January 8, 2008, by academic and industry researchers, clinicians, industry executives, venture capitalists, and representatives of government agencies, as well as trade, professional, and patient associations.
- Presentations at Personalized Medicine Subcommittee meetings on April 25, 2007; September 12, 2007; and January 9, 2008; by representatives of government agencies as well as trade and professional associations representing the biotechnology, pharmaceutical, clinical laboratory services, and venture capital industries.
- Subcommittee workshop on July 24, 2007; to obtain input on intellectual property, technology/tool development, and regulation/reimbursement issues from intellectual property lawyers and representatives from the molecular diagnostics industry and venture capital community.
- Subcommittee workshop on November 28, 2007; to obtain input on information technology, electronic medical records, reimbursement, economics, and the impact of personalized medicine on development of pharmaceuticals and medical diagnostics from representatives of pharmaceutical, diagnostics, and health insurance companies as well as experts in pharmacoeconomics, reimbursement, and health information technology.

In addition to these major forums, the PCAST subcommittee conducted telephone interviews with many additional individuals from academic institutions, medical diagnostic, direct to customer, service and imaging companies, biotechnology and related tools companies, pharmaceutical and information technology companies, insurance companies and providers, patient advocates, venture capital firms, trade and professional associations, and government agencies.

IV. Focus of Report

PCAST concluded that the essential driver for the expanding promise of personalized medicine is the development and application of genomics-based molecular diagnostics.

Molecular assays have been in use for decades as diagnostics. For example, measurement of the level of activity of a single protein molecule, Factor VIII, has long been a molecular diagnostic for the underlying genetic defect in hemophilia, while a test for the mutant *bcr-abl* gene associated with the “Philadelphia chromosome” that is characteristic of chronic myeloid leukemia is used as a molecular diagnostic for the disease.

Development of these molecular diagnostics and many others based on single-gene defects did not depend on modern genomic technologies. The Factor VIII deficiency in hemophilia was discovered by classic protein analysis, while identification of the *bcr-abl* mutation was guided by the fact that it is a DNA translocation which can be identified through classic cytogenetic analysis. However, these classical approaches to molecular diagnostics development are only truly useful and practical for diseases in which a single-gene defect results in an easily observable phenomenon such as activity of a specific protein in blood or other bodily fluid or the appearance of a gross chromosomal aberration.

Unfortunately, most human diseases, as well as the human physiological response to therapy, result from a variety of different genes acting in concert. Dissecting the complex metabolic pathways involved and identifying the responsible proteins and genes for even a single disease requires large expenditures and decades of research, with results still often elusive due to the complexities of human *in vivo* experimental manipulation. Genomics-based molecular diagnostics offer the possibility of correlating genetic profiles with disease occurrence, disease outcome, response to therapy, adverse events, and other factors, without the need to fully understand the underlying biological mechanisms – the specific genes that are involved, the impact of the genes on physiology, and the way they function in concert. Genetic profiles will also be instrumental in identifying known genes or gene variants that correlate with various disease outcomes, as well as in identifying genetic regions correlated with outcome that can be investigated for previously unknown genes. Genetic profiles will thus facilitate the development of new single gene or protein tests as well as new therapies that target the consequences of specific genetic alterations.

Because of the extraordinary potential of genomics-based molecular diagnostics to accelerate progress in personalized medicine, this PCAST report focuses primarily on the policy actions required to facilitate the development and introduction into practice of this important health care innovation. Moreover, after analyzing each of the policy areas described in the previous section, the PCAST Personalized Medicine Subcommittee prioritized three of these areas – technology/tools, regulation, and reimbursement – as the focus of its strategic policy recommendations. PCAST based this prioritization on three factors. The first factor was the magnitude of the obstacles that these areas present to the near-term development and introduction into practice of genomics-based molecular diagnostics. The second factor was the degree to which the obstacles presented, and the solutions thereto, were specific to personalized medicine and not necessarily to health care overall. The third factor was the degree to which the obstacles could be addressed by defined near-term policy actions.

In focusing on genomics-based molecular diagnostics, PCAST does not mean to discount the importance of the parallel developments in genomics-linked therapeutics. At present, however, the pace of change is most rapid, and the technological, regulatory, and reimbursement hurdles to progress are greatest, in the realm of diagnostics.

Technology and Tools

The first critical obstacle to realizing the potential of genomics-based molecular diagnostics concerns the challenges encountered in validating the genetic/clinical correlations identified through discovery research. Accelerating progress in validation requires the development of critical enabling technologies, tools, resources, and standardized methodological approaches, as well as increased investment in and prioritization of validation studies. Because of the scope and high-risk nature of this work, and the fact that the ultimate goal is the development of diagnostic tests introduced into commerce, a joint public/private sector approach appeared to PCAST as the most appropriate to address these challenges.

Regulation

The second critical challenge concerns the regulatory system for laboratory diagnostics. Historically, laboratory diagnostics have been evaluated for regulatory approval solely on their ability to measure accurately the parameter of interest (i.e., analytic validity). The clinical meaning of the test result was either entirely obvious (e.g., a positive Hepatitis C test means that a patient has Hepatitis C) or was determined by the clinician in combination with other factors (e.g. the combined use of cholesterol tests, blood pressure, stress tests, and family history to determine whether a patient should be treated to prevent cardiovascular disease). In contrast, the result of a genomics-based molecular diagnostic test may not be transparent, yet may still directly determine how a patient is treated. Accordingly, the test must not only accurately measure the genetic profile (analytic validity), but the profile must also be correlated with clinical outcome in a series of robust and reproducible clinical studies (clinical validity). This is true whether the ultimate commercial diagnostic is a genomic profile or one or more specific gene or protein tests derived from the results provided by the profile. Therefore, genomics-based molecular diagnostics need a regulatory regime that considers both analytical and clinical validity. Such a regime will require diagnostic developers to adapt to a regulatory approval pathway for diagnostics that may look more like that for pharmaceuticals. The challenge is to implement such a new regulatory approach without placing unnecessary or uncertain burdens on product development.

Reimbursement

The third critical challenge is insurance coverage and reimbursement, which must provide adequate compensation for the cost and time required to establish both analytic and clinical validity. Traditionally, laboratory diagnostics have been reimbursed based on commodity pricing of simple laboratory procedures. However, genomics-based molecular diagnostics not only involve more expensive laboratory and data analysis procedures, but also must bear the development cost for establishing clinical validation; this cost is analogous to the clinical trial costs associated with pharmaceutical product development. Therefore, a value-based coverage and reimbursement approach for these products, similar to that used for high-value pharmaceuticals, must be developed or such products may never reach patients. In addition, because reimbursement for high-value products must be driven by true clinical benefit for the covered population, criteria for demonstrating both clinical utility and validity must be developed and standardized. These criteria can then be used to guide both product development and reimbursement decisions.

Despite the focus of this report on the three challenges outlined above, the other policy areas considered by the subcommittee are clearly still relevant over the long term to the successful development and introduction into practice of genomics-based molecular diagnostics. Each of these areas is discussed briefly below.

Information Technology

Health care information technology tools, including electronic medical records, personal medical records, and clinical decision support systems will be essential enablers for the development and widespread use of genomics-based molecular diagnostics. Fully interoperable, standardized electronic medical records allow data to be readily aggregated and analyzed across multiple records. Not only will this allow physicians to have a full picture of a patient's medical history, but it may also serve as an invaluable platform for research into the correlation of genomic markers with clinical phenomena. Clinical decision support tools integrated with medical records are essential to allow physicians easy access to new patient-appropriate diagnostic tests as well as to automated resources for the interpretation of test results. Many previous policy recommendations have addressed the development of these tools, and both the public and private sector continue to make extensive efforts to address this need.

In April 2004, the President issued an Executive Order creating the Office of the National Coordinator for Health Information Technology (ONC) within HHS. The Executive Order charged ONC with providing leadership for the development and national implementation of an interoperable health information technology infrastructure and also with achieving the goal of widespread adoption of interoperable electronic health records by 2014. The ONC strategy is to collaborate with the private, nonprofit and non-Federal public sectors and incentivize investment

by those stakeholders through Federal laws, procurement contracts, conditions of doing business with the Federal Government, and reimbursement.

In September 2005, HHS Secretary Leavitt established the American Health Information Community (AHIC) within ONC as a Federal advisory committee to provide input and recommendations from the private and nonprofit sectors regarding the development of interoperable electronic medical records with appropriate privacy and security protections. AHIC has conducted extensive deliberations to develop recommendations regarding policy, technical, business, and social issues across several domains and has identified several clinical functions that should be prioritized for standards definition and electronic implementation. The ultimate goal is to facilitate the emergence of a shared, interoperable, electronic Nationwide Health Information Network which all health care providers could access. AHIC is expected to be transitioned into a sustainable public-private collaboration based in the private sector by the end of 2008.

In addition to these Federal coordination efforts, the private sector is actively engaged in developing and implementing both electronic medical records and electronic clinical decision support systems linked to such records. Integrated health care systems such as the Veterans Health Administration and Kaiser Permanente as well as major hospitals and regional medical networks have made considerable progress in implementing electronic medical record systems. However, the overall rate of adoption of electronic medical records and decision support tools remains low, in part because of the very low rate of adoption in the small group or independent physician practices that comprise the majority of practices in this country today. Recent direct-to-consumer electronic medical record product offerings by large internet-based information companies may begin to provide alternative routes for direct patient access to the creation and use of such records.

PCAST endorses and strongly encourages continued support of the important coordination and standard-setting efforts of ONC and AHIC, as well as the ongoing efforts in the private sector. Because these efforts are at an early stage, it is difficult to determine if they will address all of the important obstacles. However, until the current efforts are more fully implemented and their success can be assessed, PCAST concluded that it should not recommend additional policy actions at this time.

Intellectual Property

The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products, including genomics-based molecular diagnostics. Unfortunately, several recent events have threatened the stability of intellectual property protection in the biosciences.

Recent Supreme Court cases have made the nonobviousness standard more stringent, shed doubt on the potential to patent diagnostic correlations, expanded the activities covered by the research and development exemption, and made obtaining injunctive relief for patent infringement more difficult. The proposed Patent Reform Act of 2007 has opened a contentious debate among stakeholders from different industries concerning the impact of several elements of the Act, including the post-grant review and apportionment of damages provisions. These provisions could reduce the confidence of developers and investors in the strength of granted patents, which could be especially detrimental for the development of innovative medical products. Conversely, the opportunity to present countervailing arguments and evidence outside of litigation provided by the post-grant review provisions could reduce fears that specific molecular diagnostic products would infringe broad gene-related patents.

In August 2007, the U.S. Patent and Trademark Office published rule changes that placed new limitations on the number and nature of claims and also placed requirements on divisional and continuation applications that will likely front-load patent costs and force filing decisions before all the supporting data can be obtained. In November 2007, a Federal district court, in response to an industry lawsuit, temporarily enjoined the implementation of these rule changes. In April 2008, the court granted a summary judgment in favor of the industry challenge on the grounds that the proposed rules were “substantive in nature” and therefore the Patent Office had exceeded its rule-making authority.

The challenges posed by these major intellectual property law changes urgently require a comprehensive, cross-industry analysis. The issues are enormously complex and apply not only to genomics-based molecular diagnostics

and other personalized medicine products such as targeted therapeutics and single-gene or protein tests, but to all innovative biomedical products and products of other industries as well.

Therefore, PCAST strongly recommends that a separate PCAST subcommittee be convened to address these patent law issues across all domains and issue a report devoted exclusively to these issues. To attempt to address these complex and broadly applicable issues as only one aspect of a report focused specifically on personalized medicine would not do them justice and would obscure their overall importance.

Privacy

PCAST applauds the recent passage and signature into law of the Genetic Information Non-Discrimination Act of 2008 (GINA).²³ GINA is expected to alleviate many of the privacy concerns that have made many patients unwilling to have genomics-based molecular diagnostic or other genetic tests performed. However, even with the passage of GINA, certain privacy issues remain of concern to the public.

The first issue is the fact that detailed genetic information has the potential to uniquely identify an individual even if the data are not linked to obvious identifiers such as name, address, or social security number. As a practical matter, however, the use of genomic sequences to identify individuals would require access to a database that connects data to individuals. The relevant policy issue is the establishment and maintenance of adequate database security and controls on data use – a problem that applies to all sensitive patient data, not just to genomic sequences.

The second issue is that the potential for an unintended release of genetic information that violates patient privacy is greater if the information is stored in large interoperable electronic databases that are widely available to the research and clinical community as opposed to paper records held by individual sites. Technologies and procedures for encryption, password protection, audit trails, and transaction-specific access codes are important tools for establishing and maintaining the necessary data controls. Many security breaches, however, arise not from limitations of the technology but from improper use or malicious evasion of data controls. Achieving data security in a large organization is as much a management issue as a technical one; the challenges involved are considerable, and are beyond the scope of this study.

The third issue is that methods must be established to enable essential research on the correlation of genetic signatures with disease while preserving individual privacy. To advance personalized medicine, it will be important for researchers to be able to test stored patient specimens for new genetic characteristics that may be correlated with their clinical outcomes. Because the specific genetic tests to be performed may not be known at the time the sample is collected, it will be essential to have an informed consent process that authorizes testing of de-identified samples for genetic characteristics not anticipated at the time of collection. Such an informed consent process is included in the PCAST recommendation with regard to biospecimen repositories in the Technology and Tools section of this report.

Given the passage of GINA and the fact that other privacy concerns are either addressed by policy recommendations elsewhere in this report or are complex topics that warrant detailed analysis in their own right, no additional privacy-specific policy recommendations appear warranted at this time.

Physician and Patient Education

The education of physicians on the proper interpretation and use of data provided by genomics-based molecular diagnostic tests will be essential for the effective introduction of these diagnostic innovations into practice. Education will require not only effective clinical decision support tools, but also the inclusion of these topics into medical school and continuing medical education curricula. However, because these new diagnostic tests are only just beginning to be introduced and most of them are focused on specialty practices such as oncology and HIV treatment, the medical education experts contacted by PCAST did not yet view this area as a high priority.

²³ Public Law 110-233.

Based on this input, PCAST determined that no specific policy actions on physician education were warranted until the number of genomics-based diagnostic tests driving personalized medicine had increased. Nevertheless, current medical education practices devote little attention to new genetic and molecular technologies despite their potentially broad impact on medical practice. Nonspecialist physicians run a risk of partial disenfranchisement should the pace of translation of these discoveries continue to accelerate and should consumers play a more active role in educating themselves on these topics.

Patients and the public also need carefully positioned, realistic, and easily understood information about both the potential and the limitations of personalized medicine in general, and about genomics-based molecular diagnostics in particular. The patient advocacy community represents a strong and valuable player in this arena and PCAST supports and encourages their efforts. The National Institutes of Health (NIH), as leader of the Federal biomedical research establishment, is also very important to these education efforts as are several professional medical associations. Because of the ongoing activities of these various groups, PCAST does not believe additional broad policy actions to facilitate widespread patient education are necessary until such time as more tests are reaching the end of the development pipeline. Nevertheless, PCAST hopes that this report in its entirety helps lay a foundation for a vital educational outreach effort to the public on the realistic promise and limitations of these new diagnostic tests and of personalized medicine overall.

Economics

Finally, PCAST considered the economic perspective on personalized medicine. As with other areas of medical technology, medium- to long-term progress will depend on the economic viability of individual personalized medicine products brought to market. Each of the priority issues considered in detail in this report – the research activities required to validate genomics-based diagnostics, the regulatory process, and coverage and reimbursement policy – will have a strong impact on the cost of bringing new products to market and the likely financial return once marketing approval has been granted. In turn, these parameters will determine the attractiveness of personalized medicine to the investor community.

Economists have published a variety of theoretical economic analyses and models relevant to personalized medicine, several of which were presented to PCAST. These studies were helpful in illuminating the factors that will affect economic viability for individual personalized medicine products and the overall cost impact on health care. However, given personalized medicine's early state of development and the corresponding lack of empirical data on R&D costs, product pricing, and the clinical and economic impact of real-world use, specific conclusions that might inform public policy at the national level are difficult to draw from these models. However, PCAST encourages ongoing activities in both the private sector and Federal agencies to identify and assess economic factors that provide potential incentives and disincentives for personalized medicine products and services. Such analyses will become increasingly important as more products reach the market and related individual and societal benefits are evaluated. Otherwise, no specific policy actions with regard to the economics of personalized medicine are recommended at this time.

V. Technology and Tools²⁴

Background

Human genetic variation is what makes “personalization” of disease treatment and prevention both necessary and possible. Over the last decade, the revolution in genomic technologies has vastly increased our ability to analyze this variation, resulting in an ever-increasing number of powerful new tools for elucidating the genetics of complex diseases and traits.²⁵

Emerging genomics capabilities – especially the rapidly increasing power of technologies for gene sequencing and for the measurement of gene expression – are often identified as a key driver of personalized medicine. Yet many existing personalized medicine applications were created using less sophisticated approaches to measuring gene expression or are tests that measure the protein products of genes or other “downstream” physiologic phenomena rather than the genes themselves. For example, the significance of HER2 in breast cancer was first identified using a combination of HER2 protein assays and older methods for analyzing gene expression, and protein assays remain important in the clinical use of Herceptin® (trastuzumab). Differences in metabolism of purine drugs are known to be caused by genetic variation in the TPMT gene, but clinically this is measured by assaying the activity of the TPMT protein. Finally, the recently-introduced Trofile assay for targeting use of the novel anti-HIV agent Selzentry™ (maraviroc) is based on synthetic “pseudoviruses” that measure the ability of a patient’s HIV strain to infect cells with different receptor types. Although the construction of the pseudoviruses was dependent on advanced techniques of molecular biology, the test itself does not detect genomic variants.

The power of the new genomic technologies is that they provide the opportunity to correlate genetic variation with disease phenomena without the need to understand any of the physiological processes or proteins involved. Therefore, tests that directly measure genes or gene expression are beginning to complement previous tests, while some new personalized medicine diagnostics are solely gene-based. Moreover, genomic approaches can complement other techniques of molecular and cellular biology in developing new diagnostic tests based on proteins, single genes, or other attributes. Finally, genomic analyses of human genetic variation at the population level will likely facilitate the identification of new diagnostic markers and potentially new targets for therapy as well.

This section briefly describes several important genomic technologies and the critical technical approaches and resources needed to translate these breakthroughs into clinical benefit.

Genomic Technologies and Analytical Tools²⁶

Genomic technologies are central to the promise of personalized medicine. Current technologies include genome sequencing, analysis of genetic variation resulting from single nucleotide polymorphisms (SNPs) or changes in DNA structure, and gene expression analysis through microarrays. Moreover, new technologies are continuing to emerge rapidly.

Sequencing of the human genome provided the essential springboard for the revolution in genomics and genomic technologies. To date, sequencing has indicated that much of human genetic variation is concentrated in approximately 10 million of the 3 billion human DNA base pairs. Therefore, it has been more cost-effective to correlate genetic variation with disease based on those 10 million sites showing variation – which are often associated with SNPs – rather than to attempt to sequence and analyze the entire genome for each individual. A complementary technology – microarrays – allows the measurement of thousands of SNPs or the expression level

²⁴ Appendix C provides a glossary of terms used in this section.

²⁵ Pennisi E, “Breakthrough of the Year: Human Genetic Variation,” *Science* 2007 Dec 21;318(5858):1842-1843.

²⁶ Appendix D provides additional explanatory detail on genomic technologies and analytical tools.

of thousands of genes on a high density silicon wafer. Microarrays thus make possible not only comprehensive SNP analysis but also efficient measurement of the degree to which genetic variation is manifested in the level of the proteins produced.

At present, personal genome sequencing is not yet cost-effective as a tool for analyzing the correlation of genetics with disease. However, the cost of next-generation sequencing methods is decreasing rapidly while their quality and capability are improving. Application of these new approaches to sequencing of individual genomes has already revealed an unexpected degree of sequence variation associated with the insertion, deletion, or rearrangement of DNA sequences, some of which is associated with disease.²⁷ Based on the importance of these structural changes and the advances in sequencing technology, it is possible that sequencing of individual genomes will become the standard and routine level of analysis for DNA variation.

“A rapid pace of development, coupled with the quantitative and dynamic range aspects of next-generation sequencing technologies, are rapidly impacting the course of fundamental sequencing-based biological inquiry” – a noted researcher and leader in the field of sequencing technologies. This evolving technology landscape is discussed further in Appendix D.

Genome Sequencing

In 1988, Congress provided funding to NIH and the Department of Energy to undertake the Human Genome Project to explore the potential of fully sequencing the human genome. Advances in technology, including the development of detailed genetic and physical maps and better, cheaper, and faster technologies for handling and sequencing DNA, were key to accelerating progress.²⁸ A draft sequence covering more than 90% of the 3 billion human base pairs was completed in 2000,²⁹ and a full sequence was completed in 2003, at a total cost of about \$3 billion.³⁰ These sequences, as well as the sequence published by Celera,³¹ were mixtures of the sequences from a number of different individuals.³² This composite approach was chosen to protect privacy and to ensure that the reference sequence captured at least part of the sequence variation that was already known to exist.

Once the reference sequences were complete, several next-generation sequencing technologies were developed, supported in part by the Human Genome Technology Program of the National Human Genome Research Institute. These technologies allowed individual genomes to be sequenced in a more efficient and cost-effective manner. For example, the genome sequence of Nobel Laureate James Watson, which was announced in 2007, was completed in two months at a cost of less than \$1 million.³³

²⁷ Pennisi E, “Breakthrough of the Year: Human Genetic Variation,” *Science* 2007 Dec 21;318(5858):1842-1843.

²⁸ Collins FS. “Contemplating the End of the Beginning.” *Genome Res* 2001 May;11(5):641-3.

²⁹ Lander ES, Linton LM, Birren B, *et al.* “Initial Sequencing and Analysis of the Human Genome,” *Nature* 2001 Feb 15;409:860-921.

³⁰ Collins FS, Green ED, Guttmacher AE, Guyer MS. “A Vision for the Future of Genomics Research,” *Nature* 2003 Apr 24;422:835-47.

³¹ Venter JC, Adams MD, Myers EW, *et al.* “The Sequence of the Human Genome,” *Science* 2001 Feb 16;291:1304-51.

³² The Human Genome Project sequence was based on twelve individuals, including males and females to capture both X and Y chromosomes, while the Celera human genome sequence was a composite of sequences from five people representing European, African, American (North, Central and South), and Asian ancestries.

³³ Wheeler DA, Srinivasan M, Egholm M, *et al.*, “The complete genome of an individual by massively parallel DNA sequencing,” *Nature* 2008 Apr 17;452:872-6.

Based on the continued rapid pace of development for these technologies, in January 2008 an international consortium, including the National Human Genome Research Institute, the Wellcome Trust Sanger Institute and the Beijing Genomics Institute, announced plans to sequence the genomes of at least 1,000 individuals from around the world to capture medically relevant variation.³⁴ This “1,000 Genomes Project” is intended to capture a wide range of “genetic signatures” that distinguish populations and their specific health issues.³⁵

In the private sector, Knome, in partnership with the Beijing Genomics Institute, began in the fall of 2007 to offer whole genome sequencing and analysis services for individuals at a starting price of \$350,000.³⁶ Knome’s clients retain full ownership of their sequences, and may share all or part of their genomes with researchers and other medical professionals. The genome sequences of two individuals have been reported to be in progress.³⁷ Moreover, the X PRIZE Foundation has established a new milestone by offering a \$10 million prize for the first team that can sequence 100 human genomes within 10 days or less, with good completeness and accuracy and at a recurring cost of no more than \$10,000 per genome.³⁸ Six groups have already entered the competition.³⁹

Many expect the goal of a “\$1,000 genome” to be achieved in the near future. Moreover, complete individual genome sequences are beginning to emerge as a laboratory tool for assessing the correlation of genetic characteristics with disease, and such sequences may eventually become a diagnostic tool in the clinic.

Single Nucleotide Polymorphisms

Genome sequencing initially revealed that less than 1% of the human genome represents sites where there is significant variation across individuals. If a given single base pair variant of this type appears in at least 1% of the population, it is known as an SNP. An estimated 9-10 million common SNPs exist in human genomes.⁴⁰ In 2000, the Human Genome Project began collaborating with the SNP Consortium, a public-private partnership of ten large pharmaceutical companies and the Wellcome Trust (see box), to identify SNPs across the human genome and particularly in the coding regions of known genes. By 2001, 1.8 million SNPs had been identified and released into the public domain.⁴¹

Although in theory all common human SNPs could be identified and analyzed for correlation with disease, at present this is not cost-effective. An alternative is to identify regions of the genome, termed haplotypes, which contain multiple SNPs that are often inherited together. To that end, the International HapMap Project was launched in 2002 with the goal of identifying at least one common SNP for every 5,000 bases in the sequences of 270 individuals from four geographically diverse populations. By 2007 approximately 3.1 million SNPs were mapped, yielding a density of one SNP per 1,000 bases and capturing an estimated 25-35% of the common SNPs in the human genome.⁴² Because each haplotype can be uniquely identified by these “tag SNPs,” an individual’s haplotype profile can be determined by identifying which “tag SNPs” are present in their DNA. These haplotypes currently provide a more efficient and cost-effective method for conducting population-level studies of the association of genes with disease than does mapping of individual SNPs.

³⁴ NIH News: International Consortium Announces the 1000 Genomes Project, <http://www.genome.gov/pfv.cfm?pageID=26524516>, accessed July 18, 2008.

³⁵ <http://www.1000genomes.org/page.php?page=home>, accessed July 20, 2008.

³⁶ <http://www.knome.com/>, accessed April 24, 2008.

³⁷ Harmon A., “Gene Map Becomes a Luxury Item,” *New York Times*, March 4, 2008. http://www.nytimes.com/2008/03/04/health/research/04geno.html?_r=1&adxnnl=1&oref=slogin&adxnnlx=1216581433-lpw1XDZ/e04GtTZRaMweQA, accessed July 20, 2008.

³⁸ <http://www.xprize.org/genomics/archon-x-prize-for-genomics/prize-overview>, accessed June 30, 2008.

³⁹ Pollock A, “The Race to Read Genomes on a Shoestring, Relatively Speaking;,” *Washington Post*, February 9, 2008.

⁴⁰ The International HapMap Consortium, “A Second-Generation Human Haplotype Map of Over 3.1 Million SNPs.” *Nature* 2007 Oct 18;449(7164):851-61.

⁴¹ http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml, accessed June 30, 2008.

⁴² The International HapMap Consortium, “A Second-Generation Human Haplotype Map of Over 3.1 Million SNPs.” *Nature* 2007 Oct 18;449(7164):851-61.

Currently, DNA SNP microarrays are being used for analyzing SNP variation in genome-wide association studies and by some of the personal genome services. However, rapidly emerging sequence-based approaches may prove to be a more powerful and cost-effective alternative to microarrays.

THE SNP CONSORTIUM

The SNP Consortium was established in April 1999 as a public-private partnership to produce a public resource of human SNPs. The consortium involves the pharmaceutical companies listed below and the Wellcome Trust. The international member companies committed at least \$30 million to the project and the Wellcome Trust an additional \$14 million.

Pharmaceutical Company Partners

APBiotech, Inc. (part of General Electric Company)

AstraZeneca PLC

Bayer AG

Bristol-Myers Squibb Company

F. Hoffmann-La Roche Ltd

GlaxoSmithKline PLC

International Business Machines Corp.

Motorola, Inc.

Novartis AG

Pfizer Inc.

G.D. Searle & Company (is part of Pfizer Inc.)

SmithKline Beecham PLC (is part of GlaxoSmithKline PLC)

DNA Structural Variation

Analysis of genomic variation resulting from structural changes in DNA, including insertions, deletions, and rearrangements, has been facilitated by the ability to sequence individual genomes. These changes, which can involve from a few to thousands of bases, can increase or decrease the copy number of a particular gene, delete it altogether, or alter or eliminate its functionality (including disrupting critical regulatory elements) and thus could have profound effects. For example, it has been estimated that in some populations, copy number variation may account for as much as 20% of the difference in gene expression across individuals.⁴³ This class of genetic variation could thus form the basis of important new diagnostic tools.

Expression Microarrays

The development of the DNA microarray in the late 1980s revolutionized the ways in which gene expression could be measured, allowing researchers to assay the expression of thousands of genes in parallel instead of one or a few genes at a time. Rapid advances in technology led to commercial, high-density arrays of DNA probes on silicon wafers, commonly called “chips.” These chips can be used in the laboratory to query thousands of expression signatures for correlations with disease. When specific correlations are identified and validated, microarray chips containing appropriate sets of DNA probes can also serve as the basis for diagnostic tests suitable for use in the clinic.

⁴³ Pennisi E, “Breakthrough of the Year: Human Genetic Variation,” *Science* 2007 Dec 21;318(5858):1842-1843.

Correlating Genomic and Clinical Information

In order to translate advances in genomic knowledge into human health benefits, one must be able to link genetic variations with the risk of disease or with disease outcomes such as progression, response to therapy, or adverse events. To that end, there has been significant activity over the last several years in three critical areas – genome-wide association studies, development of molecular diagnostics (including *in vitro* diagnostic multivariate index assays or IVDMIAs), and biospecimen banking.

Genome-Wide Association Studies

Genome-wide association studies offer the potential to greatly increase the number of genomic markers that are identified as correlates of disease, and to provide new approaches for initial validation of such correlations. In these studies, a statistical approach is used to link SNPs or haplotypes, and also potentially other types of sequence variation, with disease occurrence in a population. In the most extensive such study reported to date, the Wellcome Trust analyzed samples from 2,000 individuals for each of seven diseases (for a total of 14,000 cases) against a common set of 3,000 control samples. In June 2007, they reported the statistically significant association of 24 independent genetic regions with the various diseases.⁴⁴

However, in their report the authors raised several cautionary notes about genome-wide association studies. First was the paramount importance of quality control, because small variations in DNA concentration, sampling procedures, and other factors can obscure true associations. Second, they highlighted the critical importance of statistical rigor in the selection of candidate SNPs for further rounds of analysis. Either a too lenient or a too stringent approach can lead to misinterpretation of results. Third, they demonstrated that large sample sizes are required to generate meaningful data, because the number of regions identified would have dropped dramatically if only 1,000 cases of each disease and 1,000 controls had been used. In fact, they recommended that even larger sample sizes be used in the future and that separate studies on the same trait be combined for greater reliability.

One such combination study reported in August 2007⁴⁵ confirmed one of the regions identified by the Wellcome study as associated with cardiovascular disease. However, analysis of the combined data sets did not confirm several other regions and also identified four new regions not identified in either study alone. Both reports stressed that such initial studies generate a wealth of preliminary data that must be validated in independent studies of comparable size. Both also conclude that much more work is needed to provide a basis for clinically-useful prediction of disease.

Molecular Diagnostics

The ability to generate genetic profiles using microarrays and sequence-based approaches promises to expand greatly the utility of genetic tests in clinical medicine. This is because human diseases resulting from a single genetic alteration are rare. Most common diseases including cancer, cardiovascular disease, and diabetes result from a variety of genetic changes acting in concert. Moreover, the exact combination of genetic factors resulting in a specific disease often varies among individuals. To address this complexity, many companies and academic groups are developing complex molecular diagnostics (including IVDMIA tests based on microarrays) with the goal of establishing correlations between a specific pattern of genetic modification and/or gene expression and disease outcomes such as progression, response to therapy, or adverse reactions. In some cases, these correlations and their predictive value are strong enough that the tests can have clinical utility even in the absence of a full understanding of the effects of and interactions among the component genes.

⁴⁴ The Wellcome Trust Case Control Consortium, "Genome-Wide Association Study of 14,000 Cases of Seven Common Diseases and 3,000 Shared Controls," *Nature* 2007 Jun 7;447(7145):661-78.

⁴⁵ Samani, NJ, Erdmann J, Hall AS *et al.* "Genomewide Association Analysis of Coronary Artery Disease," *New Engl J Med* 2007 Aug 2;357(5):443-53.

As with genome-wide association studies, there are many pitfalls in establishing robust and reliable disease correlations for genomic profiling tests.^{46, 47} Reproducible sample collection and processing is essential to avoid artifacts in gene expression patterns due to cell population subtypes or effects of processing on the apparent levels of expression. Standards for the measurement, analysis, and reporting of biomarker data are essential to allow data to be compared across different studies and different laboratories and reduce duplication in defining assay methods and data requirements. Complicated statistical methodologies are required because probing the expression of 10,000 or more genes can lead to spurious correlations simply by chance. Moreover, these studies require not only large sample sizes but also validation using independent sample sets.

Biospecimen Banks

Biospecimen banks are repositories that collect, store, process, and distribute biological materials and the data associated with them. The biological materials collected by these repositories typically include DNA, cells, tissues, and blood, though other biological samples may also be collected for specialized purposes. In most instances, the specimens are associated (annotated) with medical and demographic information and sometimes lifestyle and environmental information as well. Banks can be established in several different formats and serve different purposes.

Longitudinal population cohort banks contain samples collected over time from a defined group of individuals who are representative of a population but not necessarily a disease. These banks can be used to study the natural occurrence and progression of disease and to validate whether proposed genetic risk factors have a real-world impact on the disease in that population. Examples of such longitudinal banks include those associated with the Framingham Heart Study,⁴⁸ a group of banks containing over 800,000 specimens collected from 13 different U.S. cohort studies⁴⁹ and the various national biobanks currently being established including the Swedish National Biobanks program,⁵⁰ the UK Biobank,⁵¹ bancoADN (Spain),⁵² and CARTaGENE (Canada).⁵³

Clinical case/control banks contain samples from studies in which a population group with a particular disease is compared to a demographically similar group that does not suffer from the disease. The Wellcome Trust Case Control Consortium samples represent the largest of such banks although several smaller studies have been conducted for specific diseases. These banks are primarily useful for identifying and validating specific genetic loci that are associated with a disease. However, they can be converted into a case/control longitudinal cohort bank by continuing to follow both the disease and control populations over time. This conversion allows chronic disease profiles to be identified against a background of normal variation and also allows the correlation of specific genetic loci with disease progression, mortality, and response to therapy.

Disease-specific biospecimen banks differ from the above-described banks in that they include only specimens from patients with a specific disease and are continually expanded by the addition of specimens from new patients. These banks are most typical in the area of cancer where clinically and demographically annotated tumor tissue banks have been established for decades, using specimens drawn primarily from patients involved in cancer clinical trials. Banks of this type were instrumental for the studies validating the ability of the 21-gene *Oncotype DX*[®] test to predict distant recurrence and the benefit of chemotherapy in hormone-treated, estrogen-receptor positive

⁴⁶ Simon R, Radmacher MD, Dobbin K, McShane LM. "Pitfalls in the Use of DNA Microarray Data for Diagnostic and Prognostic Classification," *J Natl Cancer Inst* 2003 Jan 1;95(1):14-8.

⁴⁷ Ransohoff DF. "Rules of Evidence for Cancer Molecular-Marker Discovery and Validation," *Nat Rev Cancer* 2004 Apr;4(4): 309-14.

⁴⁸ <http://www.nhlbi.nih.gov/about/framingham/index.html>, accessed July 20, 2008.

⁴⁹ Willett WC, Blot WJ, Colditz GA *et al.* "Merging and Emerging Cohorts: Not Worth the Wait," *Nature* 2007 Jan 18;445(7125):257-8.

⁵⁰ <http://www.biobanks.se>, accessed June 30, 2008.

⁵¹ <http://www.ukbiobank.ac.uk/>, accessed June 30, 2008.

⁵² <http://www.bancoadn.org/en/home.htm>, accessed June 30, 2008.

⁵³ <http://www.cartagene.qc.ca/accueil/index.asp?l=e>, accessed June 30, 2008.

breast cancer.⁵⁴ However, many of these historical banks suffer from incomplete clinical annotation; inconsistent quality due to nonstandardized sample collection, processing, and storage; and lack of informed consent for further genetic research studies. Moreover, unlike samples from population studies, which can be collected repeatedly over time, tumor specimens have a finite volume and therefore are eventually depleted.

Regardless of the purposes for which a bank is established, their utility depends on standardized collection, processing, and storage of the biological specimens as well as on efficient mechanisms for sharing samples and information across the biomedical research community. Based on these considerations, and recognizing that the lack of standardized, high-quality biospecimens is a significant roadblock to progress in cancer research, the National Cancer Institute (NCI) established the Office of Biorepositories and Biospecimen Research (OBBR) to guide, coordinate and develop the institute's biospecimen resources and capabilities.⁵⁵ OBBR is developing and implementing standards for specimen collection, processing, and storage and promotes specimen and data sharing to facilitate high-throughput genomic and proteomic studies.⁵⁶ In addition, the NCI has established a series of awards to the Clinical Trials Cooperative Groups to ensure that high-quality standardized biospecimens are collected from NCI-supported Phase III cancer clinical trials and made available to the research community. On the international front, the Organization for Economic Cooperation and Development (OECD) began a study in 2001 which led to the June 2007 publication of the OECD Best Practices Guidelines for Biological Resource Centres.⁵⁷

Challenges

Despite tremendous excitement about the potential value of molecular biomarkers such as SNPs and microarray expression profiles as genetic disease signatures on which to base improved diagnosis, therapy, and prevention, this potential has largely gone unfulfilled. While an increasing number of candidate biomarkers are being identified, development of these biomarkers into diagnostic tests with clinical utility has proceeded at a slow pace. Bottlenecks in validation are the most important constraint on progress.

Validation must occur on two levels. The first level is confirmation that the correlation initially observed, whether through a genomics-based population study or a study based on biospecimens, is indeed real rather than a statistical artifact. This level of validation is achieved by repeating the preliminary analysis on an independent population or biospecimen sample set. The second level of validation is to confirm that use of a diagnostic test based on the correlation actually results in improved clinical outcomes for patients. This definitive validation requires a prospective clinical trial.

Correcting the current imbalance between discovery of candidate biomarkers and validation of their clinical utility will require addressing two overarching challenges. The first is more effective coordination and prioritization of public and private-sector validation research, and the second is improvement of the tools used for validation studies.

Coordination and Prioritization of Public/Private Investment

Without the large government and private investment over the last decade in the development and application of genomic technologies, modern, genetically-based personalized medicine would not be possible. However, these technologies are now mature, and although there are certainly advances still to be made, the real challenge is to fund research that reaches beyond the ability to discover genetic signatures that may be associated with disease to the validation of those associations as a basis for development of new diagnostics, therapeutics, and preventive

⁵⁴ Paik S, Shak S, Tang G, *et al.* "A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer," *New Engl J Med* 2004 Dec 30;351:2817-26; Paik S, Tang G, Shak S *et al.* "Gene Expression and Benefit of Chemotherapy in Women with Node-Negative, Estrogen Receptor-Positive Breast Cancer," *J Clin Oncol* 2006 Aug 10;24:3726-34.

⁵⁵ <http://biospecimens.cancer.gov/biospecimen/about/index.asp>, accessed June 30, 2008.

⁵⁶ http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf, accessed June 30, 2008.

⁵⁷ http://www.oecd.org/document/36/0,3343,en_2649_34537_38777060_1_1_1_1,00.html, accessed July 18, 2008.

strategies. Validation studies are part of the general area of biomedical research often termed “translational research,” which has many of the attributes of the development side of R&D. As a result, it has been historically the purview of industry rather than of government-supported academic science, which focuses on discovery.

However, because validation of genomic correlations with disease remains both expensive and high-risk, industry may not be willing to invest substantially until a clearer path to validation has been developed and a larger number of success stories achieved through the use of public funds. Therefore, to realize the benefit of public investment in genomic technologies, public investment in translational research to validate these correlations must be increased and coordinated with investment from industry to move genomic discoveries to practical application. This will require a reevaluation of the proper balance of public investment in genomic discovery versus translation of those discoveries into patient and public benefit and the development of new ways to prioritize and coordinate public/private funding.

Development of Key Translational Tools

To realize the promise of genomic technologies for the advance of personalized medicine, significant investment will be required in the development of three key translational research tools: (a) disease-specific biospecimen banks for correlating genetic variation with disease outcomes and response to therapy; (b) development of study designs addressing biomarker standardization and incorporating sophisticated statistical methods for demonstrating the clinical validity and utility of genomic profiles; and (c) population cohorts and associated biospecimen repositories for longitudinal health and disease studies.

Disease-Specific Biospecimen Banks

Correlation of specific patterns of gene modification or expression with disease outcomes requires large numbers of samples from patients with a specific disease which have been collected, processed, and stored under standard conditions with comprehensive clinical annotation and follow up. Independent, equally large specimen sets are required for validating those correlations. To be most useful, the banks should include samples collected from a wide range of patients in both academic and community settings, be continually replenished with samples from new patients, be readily accessible to researchers for a wide range of studies under appropriate review and approval processes, and be fully consented by the donors for use in genetic research studies.

Study Design

The need to analyze large, comprehensive genomic data sets in order to identify and validate genes that have a statistically significant correlation with complex disease traits presents significant challenges for study design. Many of the necessary standards for the measurement, analysis, and reporting of biomarker data have not yet been developed, while existing standards have been implemented inconsistently. In addition, the required statistical methods are more sophisticated than would typically be necessary in a clinical trial. The absence of necessary standards and the cost and high risk of these studies may deter industry from investing in the development of products based on genetic correlations until robust study designs incorporating adequate biomarker standardization and the necessary statistical methods are developed and tested through publicly sponsored studies.

Population Cohorts and Biospecimen Banks

Validation of correlations discovered through genome-wide association studies requires biospecimen samples from large population cohorts with full medical, demographic, familial, lifestyle, and occupational annotation. To meet this need, it has been proposed that a broadly representative national cohort of several hundred thousand North Americans be established.⁵⁸ Such a bank is envisioned to have comprehensive disease and environmental annotation; standardized sample collection, processing, and storage; and full informed consent for genetic studies. It would thus be the U.S. equivalent of banks being developed in other countries⁵⁹. Because this cohort bank will

⁵⁸ Collins, FS, Manolio, TA. “Merging and Emerging Cohorts: Necessary but not Sufficient,” *Nature* 2007 Jan 18;445(7125):259.

⁵⁹ See footnotes 50-53.

be expensive to develop and likely not available for use for a decade, it has also been proposed that banks from existing large cohort studies should be pooled and made available for use in near-term studies.⁶⁰ However, such a pooled bank would not be as representative of the U.S. population and its utility may be hampered by nonstandard data collection.

Policy Recommendations

PCAST makes the following policy recommendations with regard to Technology and Tools for personalized medicine.

Recommendation 1. The Federal government should develop a strategic, long-term plan that coordinates public and private sector efforts to advance research and development relevant to personalized medicine.

Recommendation 1a. Create a public/private sector “roadmap” for coordinating discovery and translational research in personalized medicine.

The Federal government, through the leadership of HHS, should join with the private sector to create a coordinated “Personalized Medicine R&D Roadmap” for translating discoveries made through advances in genomic technologies into diagnostics, therapeutics, and preventive strategies that impact human health. This roadmap will involve three key elements.

The first key element is to identify key resources and tools in need of development and determine which are best developed by the private sector, by the public sector, and by private/public collaboration. For example, because of their fundamental importance in identifying and validating genomic correlations, population and case/control cohorts and their associated biospecimen banks, as well as disease-specific banks, should be developed with public and foundation funding. In contrast, advances in high-throughput diagnostic chip technology should be the responsibility of the private sector.

The second key element is the identification of activities that should be undertaken by academic scientists with government or foundation support, those that should be pursued by industry, and those that are best done through academic-industry-government-foundation collaborations. It is generally accepted that the public and not-for-profit sectors have primary responsibility for the support of discovery science, which in the case of personalized medicine is the discovery of candidate genomic biomarkers that appear to correlate with disease. In contrast, once the correlation between a genomic profile and a disease or disease outcome has been validated, development and definitive clinical testing of a new diagnostic test or genomic-tailored therapy based on that correlation is primarily the realm of industry. However, the appropriate balance of public/private activity in conducting the translational research required to validate the correlation of biomarkers with disease is less clear, and thus requires careful attention by both public and private stakeholders.

The third key element is the establishment of public/private partnerships to support key discovery and translational research endeavors that are essential to the development of personalized medicine products and services but that are not uniquely directed at a specific commercial product. An example is the government-industry consortium proposed by the NCI Translational Research Working Group⁶¹ to fund an integrated national network of biospecimen repositories for cancer research served by a common infrastructure similar to the National Biospecimen Network Blueprint concept⁶² piloted by NCI.

⁶⁰ Willett WC, Blot WJ, Colditz GA *et al.* “Merging and Emerging Cohorts: Not Worth the Wait,” *Nature* 2007 Jan 18;445(7125):257-8.

⁶¹ <http://www.cancer.gov/aboutnci/trwg/finalreport.pdf>, accessed July 18, 2008.

⁶² <http://biospecimens.cancer.gov/nbn/blueprint.asp>.

Recommendation 1b. Evaluate the allocation of government funding to discovery versus translational research relevant to personalized medicine.

NIH and other agencies such as the Departments of Energy and Defense should evaluate their allocation of resources to basic genomic discovery research relative to the research necessary to translate genomic findings into new products and services. Such an evaluation is necessary to manage allocation of scarce government resources to assure that while important genomic discoveries continue to be made, those with the highest probability of meaningful impact on human health are translated from the laboratory to clinical testing where the correlation of genetic signatures with disease can be validated.

Arriving at an appropriate allocation of funding between discovery and translation will require a reliable method for identifying promising discoveries that are in need of translational investment and an approach for identifying ongoing projects that are aimed at translating genomic discoveries toward clinical validation. If the scale of translational effort is such that discoveries are accumulating with little hope of moving forward in a timely fashion, then a re-allocation of funds from discovery to translation must be considered. This allocation is likely to vary over time as available opportunities in discovery and in translation evolve.

Recommendation 1c. Identify national priorities for development of molecular diagnostics.

Under HHS leadership, NIH should develop a coordinated process to identify and prioritize diseases and common therapies that would benefit from the application of molecular diagnostics, taking into account both scientific opportunities and public health needs. Development projects aimed at these prioritized opportunities would provide an avenue for establishing requirements and best practices for the sample sizes, study designs, and statistical methodologies necessary to validate genetic correlations with disease and disease outcomes.

Although such projects could be undertaken solely by industry, collaborations between academia, industry, and government, such as the TAILORx trial, might be the most efficient approach for these prioritized demonstration projects. To that end, NIH should consider establishing a new award mechanism specifically to fund academic/industry collaborative projects addressing these prioritized opportunities. The awards would ideally require active participation and cofunding of the research by the industry partner. HHS should also consider establishing a “Science Prize” and an expedited FDA review process for successful projects.

Recommendation 2. The Federal government should make critical near-term investments in the enabling tools and resources essential to moving beyond genomic discoveries to personalized medicine products and services of patient and public benefit.

Recommendation 2a. Create an integrated, national network of standardized biospecimen repositories.

NIH should lead, stimulate, and coordinate public and private sector efforts to develop an integrated nationwide network of standardized biospecimen repositories to support research in personalized medicine. This network should encompass specimens from large population cohorts and case/control studies on specific diseases as well as disease-specific banks and should include banks funded by government, foundations, and industry. Such a national network will require both a comprehensive database of available samples and a transparent review process for granting access to specimens based on scientific merit and clinical potential of the studies proposed.

NIH should promote and facilitate the establishment and implementation of standards for collection, processing, storage, clinical annotation, and distribution of samples by the network, building on ongoing efforts such as the First Generation Biorepository Guidelines issued by the NCI OBBR. NIH should also continue its efforts led by the NCI to develop a standard, informed consent template that will allow continued collection of data from specimen donors (e.g. epidemiological and outcomes data) beyond the date of sample collection and authorize testing of samples for genetic and other characteristics not anticipated at the time of collection.

Recommendation 2b. Develop study designs incorporating adequate biomarker standardization and statistical methods sufficient for validating the clinical utility of molecular diagnostics.

NIH should develop a funding program for academic/industry collaborative projects addressing biomarker standardization, statistical methods and other aspects of study design necessary for validating the clinical utility of molecular diagnostics based on genomic correlations with disease characteristics. The goal of such

projects would be fourfold: (a) to develop standards for the measurement, analysis, and reporting of biomarker data, (b) to define appropriate statistical methods for analyzing complex genetic correlations, (c) to define other study design parameters required to establish clinical validity and utility, and (d) to test these study designs on specific, real-world validation challenges. If standard approaches can be developed and shown to be successful, this would reduce the uncertainty of product development and encourage further industry investment in this emerging class of products.

Recommendation 2c. Develop a large population cohort for investigating genetic and environmental health impacts.

NIH should develop a program that enrolls and follows over time a large, representative sample of the U.S. population. Participants would provide family and medical histories, lifestyle and environmental information, and biospecimens fully consented for future research. Participants would also agree to periodic followup at which time new medical, lifestyle, and environmental information and biospecimens would be collected. This program would provide a comprehensive, high quality population resource that would not only enable investigators to identify potential genomic correlations with disease but also be of sufficient size to provide independent population sets for validating the correlations. Because of the size and long-term nature of such an endeavor, consideration should be given to establishing a consortium of government, industry, and philanthropic partners to fund the program through the Foundation for the National Institutes of Health. The goal should be to create an endowment that will assure stable funding across administrations and financial cycles.

VI. Regulation

Background

Regulation of *in vitro* diagnostics in the United States is split between two agencies – the FDA, operating under its authority to regulate medical devices, and the Centers for Medicare and Medicaid Services (CMS), operating under the authority of the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Unfortunately, these long-established regulatory systems are ill-equipped to deal with complex, high-value tests that draw on cutting-edge genomics technology to directly inform high stakes clinical decisions.

Role of FDA

FDA regulation of medical devices addresses the inherent safety and efficacy of the device as well as quality control in manufacturing the device. Depending on the risk attributed to a particular product, FDA's initial evaluation of new medical devices (including *in vitro* diagnostic tests) for safety and efficacy may be limited to verification of substantial equivalence to an existing ("predicate") device or may extend to an extensive premarket approval (PMA) process. The PMA process is required for devices that are considered "high risk", which is defined by the FDA as those that support or sustain human life, are of substantial importance in preventing impairment of health, or which present a potential, unreasonable, risk of illness or injury.⁶³ Although this principle of risk-based classification is well-established, the application to *in vitro* diagnostic tests, where the purpose of the product is to provide information to the physician rather than to treat the patient directly, has been less clear.

Many of the challenges involved in defining risk for *in vitro* diagnostic tests (when categorized as devices) are analogous to those raised by certain types of medical software, such as expert systems or clinical decision support programs. In both cases, the output is information for the clinician rather than a treatment applied directly to the patient. In preparation for a workshop on software policy convened by FDA and the National Library of Medicine in 1996, FDA held discussions with a variety of medical organizations and other professional and industry sources to identify criteria that might be useful for developing measures of risk for the information generated by medical software.⁶⁴ It is noteworthy that as of this writing, in mid-2008, FDA still has not resolved either the definition of risk applicable to information generated by medical software, nor arrived at a clear policy regarding its regulation of such software.⁶⁵

Regulation of *in vitro* diagnostic tests has been further complicated by the fact that the tests may be implemented in two different ways: as preassembled kits sold to clinical laboratories by manufacturers, or as laboratory-developed tests (LDTs or "home brew" tests) performed by individual clinical laboratories from available reagents and other ingredients, for use exclusively in that laboratory. FDA considers both preassembled kits and LDTs to be medical devices subject to its jurisdiction.

In the face of pressing demands on its limited resources, FDA has exercised "enforcement discretion" (i.e., it has chosen not to exert its regulatory authority) with respect to a large group of LDTs deemed low risk. This practice is expected to change based upon FDA's Draft Guidance on IVDMIAs issued July 26, 2007.⁶⁶ However, just as for medical software that generates information as its product, FDA has not yet issued an operational definition of risk

⁶³ [PMA] Overview, <http://www.fda.gov/cdrh/devadvice/pma/>, accessed May 14, 2008.

⁶⁴ Food And Drug Administration & National Library of Medicine, Software Policy Workshop, September 3 and 4, 1996; summary notes accessed June 26, 2008 at <http://www.netreach.net/~wmanning/fdaswsem.htm>.

⁶⁵ While this report focuses on personalized medicine, PCAST notes with concern the potentially broad impacts across biomedical research of FDA's failure to clarify its regulatory approach to software.

⁶⁶ "Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays" Draft guidance provided by the Food and Drug Administration, accessed September 1, 2008 at <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>.

that would provide an unambiguous guide to the likely risk classification of new genomics-based *in vitro* diagnostic tests. In addition, FDA has not provided an unambiguous statement of the scientific evidence that would be regarded as “providing a reasonable assurance that the device is safe and effective for its intended use or uses” for those tests deemed high-risk and thus subject to the full regulatory review of the PMA process.

FDA’s exercise, over a period of many years, of enforcement discretion with respect to LDTs has had consequences for diagnostics development strategies. Test developers have adopted market entry strategies that rely on implementation of innovative molecular diagnostics as LDTs rather than as kits, thus gaining market access with a relatively low regulatory burden.

Role of CMS/CLIA

By Federal statute, a clinical laboratory may not receive specimens derived from the human body for laboratory examination unless the lab is certified as complying with the performance standards embodied in CLIA regulations. CLIA addresses personnel qualifications, quality control standards, documentation, and validation, imposing requirements that vary with the complexity of the test and its procedures. For most tests classified as “high-complexity,” requirements include periodic proficiency testing, with details governed by the specialty and subspecialty to which a given test belongs (e.g., microbiology/bacteriology or diagnostic immunology/syphilis serology). For tests in areas in which a formal CLIA specialty with associated proficiency requirements does not exist, laboratories are expected to exercise their own judgment in maintaining quality assurance and quality control programs that are “adequate and appropriate for the validity and reliability of the laboratory examinations.”

Relationship between FDA and CLIA Regulation

Assessment of new products prior to marketing is a core function of FDA regulation of medical devices. By contrast, CLIA is fundamentally a quality control system. It focuses on the proper implementation of well-established procedures and is not designed to cope efficiently with innovations that do not fit within existing specialty boundaries.

For the most part, FDA and CLIA play complementary roles. However, FDA’s oversight of quality control in the manufacture of both preassembled test kits and, as expected based upon July 2007 Draft Guidance, LDTs potentially imposes redundant requirements on the production of LDTs in laboratories subject to CLIA oversight. FDA has announced its intent to issue guidance to assist laboratories in meeting these requirements, and has invited input on coordination of FDA and CLIA requirements.

FDA’s Response to Emerging Genomics-Based Molecular Diagnostics

FDA has achieved three noteworthy milestones in regulation of *in vitro* diagnostic tests based on emerging genomics technologies, including a concept paper on drug-diagnostic codevelopment,⁶⁷ a draft guidance on IVDMIAs,⁶⁸ and a guidance on voluntary pharmacogenomic data submissions.⁶⁹ In particular, the guidance on pharmacogenomic data submissions clearly defined FDA’s intended use of such data and their status relative to the regulatory process. Among the other benefits of such voluntary submissions, FDA has noted that they provide “an opportunity for sponsors to impact FDA’s thinking and help build consensus around future pharmacogenomic standards, policies, and guidance.”⁷⁰

The FDA’s process of issuing draft guidance on IVDMIAs stimulated extensive dialog both within the private sector and between the private sector and FDA. Recognizing the promise of genomics for the development of

⁶⁷ Drug-Diagnostic Co-Development Concept Paper (draft), Food and Drug Administration, April 2005, <http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf>, accessed May 14, 2008.

⁶⁸ Draft Guidance for Industry, Clinical Laboratories, and FDA Staff In vitro Diagnostic Multivariate Index Assays, Food and Drug Administration, July 26, 2007, <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>, accessed May 14, 2008.

⁶⁹ Guidance for Industry: Pharmacogenomic Data Submissions, Food and Drug Administration, March 2005, <http://www.fda.gov/cber/gdlns/pharmdtasub.pdf>, accessed May 14, 2008.

⁷⁰ Genomics at FDA: Voluntary Genomics Data Submission (VGDS), <http://www.fda.gov/cder/genomics/VGDS.htm>, accessed May 14, 2008.

innovative diagnostic tests, scientists and investors have created many new ventures aimed at developing and commercializing a wide range of tests based on IVDMIAs and invested substantial resources in these ventures. Based on FDA's longstanding decision to exercise enforcement discretion with respect to LDTs, many developers have already launched or have planned to implement new IVDMIA diagnostic tests as LDTs rather than as manufactured kits. Thus, a number of business plans were based on a path to market via laboratory-based implementation and CLIA regulation, rather than the path of a PMA submission to FDA, which is perceived to be riskier and more costly.

The IVDMIA draft guidance changed the IVDMIA development picture in two key respects. First, it implied a substantially increased overall regulatory burden. The increase would arise largely from hurdles imposed by FDA with respect to clinical efficacy such as new requirements for prospective clinical trials, but also in part from the imposition by FDA of quality system requirements for test manufacture that appeared to be duplicative of regulations already imposed on those labs performing LDTs under CLIA. Second, residual ambiguity in the FDA's definitions of an IVDMIA and of risk left considerable uncertainty about the agency's likely response to specific new products in or planned for development. For developers, the expected effect of these changes was increased cost, time, and risk for bringing a new product to market, effectively raising the hurdle for market access and putting in question the viability of the entire sector as a target for investment.

Ongoing discussions between the private sector and FDA concerning its draft guidance on IVDMIAs have sought to clarify the remaining definitional ambiguities as well as to resolve apparent overlaps between FDA and CLIA requirements to more effectively meet the objective of preserving patient safety while not imposing unnecessarily burdensome regulation on these innovative diagnostic products. In addition, these discussions have provided the opportunity for the private sector to apprise FDA of the extent of product development activity in this area, underlining the importance of achieving clarity on regulatory policy while providing a basis for FDA to project likely demands on its resources.

Molecular Diagnostics Linked to Therapeutic Products

A diagnostic test that differentiates patients according to their likely response to a therapeutic agent defines the clinical utility of the agent, and thus has implications for labeling of the therapeutic product. When the diagnostic test and the therapeutic agent are being developed at the same time, coordination of the two development and regulatory processes may reduce cost and at the same time achieve more timely access to market for both products. However, such coordination may also pose methodological challenges.

When clinical studies are used to obtain information simultaneously on the clinical utility of both the diagnostic test and the therapeutic agent, special care is required in study design to assure that the results are statistically valid. In addition, regulatory review will engage more than one of the FDA's divisions, the Center for Devices and Radiological Health for the diagnostic and the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research for the therapeutic agent. Depending on the way in which the two products will be marketed, the FDA Office of Combination Products may be involved as well.

When different companies are developing the products, as is the case with all linked diagnostics brought to market to date as well as many that are currently in development, the situation is especially complicated. The commercial interests of the two parties will likely be very different, and FDA decisions about the exact wording of product labeling may have broader implications. The interests of the therapeutic developer will generally be best served by competition that increases the availability and reduces the cost of the linked diagnostic. On the other hand, the interests of the diagnostic developer are generally best served by labeling that recommends or requires the use of the specific diagnostic product and thereby sustains pricing power. Thus, the economics of the therapeutic and diagnostic products as well as the cost and timing of bringing competing diagnostics to market is affected by whether the FDA identifies a related diagnostic product in the therapeutic product's label by brand name or simply by generic type. In addition, the therapeutic product developer may be concerned about product approval being delayed or approved indications circumscribed because of the actions of the diagnostic company.

Approved labeling for drugs that are already marketed may also be revised to reflect emerging knowledge from new diagnostic tests. The resulting more effective use of existing drugs is an important part of the promise of personalized medicine. As with diagnostic and therapeutic products that are codeveloped, the key challenges in such relabeling are associated with the diagnostic test and its validation. In August 2007, as a result of emerging

knowledge on the role of genetic factors in the metabolism of warfarin, FDA revised the approved product label to include background information about two genetic factors, for which tests are now available, that may affect a patient's response to the drug. However, FDA did not change the indications for the drug or recommend that physicians test routinely for these factors before prescribing warfarin. Such a label change is unlikely until a prospective clinical trial has verified that routine use of the tests delivers measurable and meaningful clinical benefits. On the other hand, in July 2008, FDA issued an alert and announced a forthcoming change in product labeling to recommend that all patients who are being considered for treatment with the anti-HIV agent abacavir be screened using one of the available genetic tests for the HLA-B*5701 allele. In this case, FDA judged that two clinical studies provided compelling evidence of the clinical benefit of such screening.⁷¹

The Critical Path Initiative

The number of innovative drugs, biologics, and medical devices submitted for FDA approval in recent years has not kept pace with the accelerating progress in fundamental science. Many observers in both the public and private sector believe that this gap is evidence that the development path for drugs and devices has become increasingly challenging, inefficient, and costly.

Responding to this concern, FDA launched the Critical Path Initiative in 2004 as "FDA's 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." As noted by FDA, "the goal of the Critical Path Initiative is to bring new scientific discoveries – in fields such as genomics and proteomics, tissue engineering, imaging, and bioinformatics – to bear on product development, to improve the accuracy of the tests we use to predict the safety and efficacy of investigational medical products."⁷²

Innovative biomarker tests, including genomics-based molecular diagnostics, have been identified as a key focus of the Critical Path. As described above, these tests offer promise in several respects:

- They may make it possible to identify patient subpopulations that are more likely to respond to a new treatment, thus enabling smaller, faster, and less expensive clinical trials.
- They may facilitate earlier identification and more effective management of safety or toxicity issues.
- It may be possible to use tests for certain biomarkers as surrogate measures that predict the effectiveness of a treatment well before the outcome of interest (e.g., improved survival) can be observed directly. Use of such surrogate measures could enable faster clinical trials and shorten the time to market for new drugs.

The Critical Path Initiative is being implemented through a series of workshops, standard-setting activities, and targeted research projects that are often conducted in collaboration with academia and industry. However, to date, progress on the Critical Path has been slow, in part because of inadequate funding. Creation of the Reagan-Udall Foundation under the Food and Drug Administration Amendments Act of 2007 is intended to advance the Critical Path Initiative, though initial funding and operational launch of the foundation has been slowed by an unresolved political dispute within Congress.

The FDA and Clinical Decision Support

Over the long term, widespread adoption of genomics-based diagnostics may be affected by whether and, if so, how computer-based clinical decision support systems are regulated as medical devices by the FDA. A heavy-handed regulatory approach could severely inhibit both their initial development and manufacturers' ability to keep pace with rapidly changing clinical knowledge, thus serving as a disincentive to investment. In turn, delays in the development of clinical decision support systems could slow the adoption of many personalized medicine products.

⁷¹ Information for Healthcare Professionals – Abacavir (marketed as Ziagen) and Abacavir-containing medications, <http://www.fda.gov/cder/drug/InfoSheets/HCP/abacavirHCP.htm>, accessed August 9, 2008.

⁷² Critical Path: Frequently Asked Questions, <http://www.fda.gov/oc/initiatives/criticalpath/faq2.html>, accessed July 18, 2008.

Challenges

Timely and effective adaptation to technological change can be a major challenge for regulatory agencies, which are typically short of resources to meet their existing responsibilities. But the application of outdated regulatory approaches can impede innovation by inappropriately delaying or denying access to market, harming manufacturers and patients by denying access to beneficial new technologies. On the other hand, regulatory standards and procedures that fail to address new hazards may subject patients to risk that is disproportionate to the benefit of the product or service. Finally, inadequate public understanding of the risk/benefit tradeoffs are inherent in all medical products; unrealistic expectations for absolute product safety can severely complicate the political environment in which the regulatory system must function. Although achieving the appropriate regulatory balance for emerging medical technologies is not easy, it is essential if the nation is to realize the benefits of its investments in biomedical research.

The FDA has made considerable progress in defining its approach to the regulation of *in vitro* diagnostic products based on emerging genomic technologies. Nevertheless, FDA guidance remains ambiguous or incomplete in several important areas:

- The criteria that define risk for products where information is the key result or output from use of the product
- Risk classification of new diagnostics for regulatory purposes
- Standards for PMA review of new medical devices, including standards for study design and conduct and standards for product performance⁷³
- Reconciliation of potentially redundant requirements between FDA and CLIA
- The regulatory approach to codevelopment of diagnostics and therapeutics
- Standards and approaches for adjusting therapeutic product labeling to incorporate use of diagnostics
- FDA's regulatory approach to IT-based clinical decision support systems
- Timely guidance on emerging innovative technologies relevant to *in vitro* diagnostics

Policy Recommendations

Recommendation 3. FDA should implement a more transparent, systematic, and iterative approach to the regulation of genomics-based molecular diagnostics.

- **IVDMIA.** In finalizing its IVDMIA guidance, FDA should further clarify its definition of risk, defining specific risk criteria for IVDMIAs in light of their intended uses and providing illustrative examples distinguishing products that will be subject to full PMA review from those that will not. At the same time, such guidance should allow an adequate transition time for existing product manufacturers, as well as those currently developing new products in the midst of regulatory change.
- **Coordination of FDA and CLIA requirements.** FDA and CMS should identify in a timely manner all aspects of overlap and potential redundancy in their oversight of LDTs and issue guidance to clarify the relationship between their respective requirements and eliminate redundant requirements.

⁷³ In its overview of *in vitro* diagnostics regulation, FDA cites three limitations to its review of PMA applications: lack of a “gold standard” against which to judge performance, the potential for bias in the collection of safety and efficacy data due to problems in study design or conduct, and the fact that “it can be challenging to determine the minimum performance required for approval.” <http://www.fda.gov/cdrh/oivd/regulatory-overview.html>, accessed April 1, 2008.

- **Co-development.** FDA should further develop its draft concept paper on drug-diagnostic co-development into a definitive guidance on the topic, reflecting the principles of clarity in requirements and standards and transparency in regulatory procedures. In particular, wherever it is scientifically reasonable, FDA should specify standard approaches to study design that will be considered appropriate for particular types of co-developed products, while accommodating alternative approaches if justified.
- **Labeling of therapeutic products.** FDA should clarify its criteria and procedures for determining when the labeling of a therapeutic product will be changed to incorporate information on related diagnostic tests and its criteria for determining how that information will be used – when it will be incorporated purely as background information, as for example in the recently-updated labeling for warfarin;⁷⁴ when it will be used to recommend specific action by physicians, as in the forthcoming revised labeling for abacavir,⁷⁵ and when it will become part of the product indication, as for example in the labeling for Herceptin® (trastuzumab).⁷⁶
- **Clinical decision support.** FDA should specify its intended approach to the regulation of automated clinical decision support systems, restricting its oversight to those aspects of performance and safety that specifically arise from the use of hardware and software (e.g., identifying and preventing failure modes that arise from particular technical approaches). As is well-established practice, responsibility for clinical content should rest with the professional bodies that create the content.
- **More systematic interaction and guidance.** In gathering information for regulatory policy development, FDA should enhance communication with affected constituencies by issuing more frequent and timely Requests for Information and draft guidance documents. In consultation with government, academic, and industry scientists, FDA should issue frequently updated guidance documents addressing regulatory issues relevant to genomics-based molecular diagnostics, including risk classification and standards for clinical study design and for analytic and clinical validity that must be met for product approval and for labeling changes.

Recommendation 4. The FDA Critical Path Initiative should be adequately funded to support its envisioned research efforts that are critical to the progress of personalized medicine.

- Projects that should be prioritized include research and development on the use of biomarkers to facilitate product development and regulatory review and the development of standards for clinical trial design and biostatistical analysis in the validation of innovative molecular diagnostics.
- In support of the Critical Path Initiative, launch of the Reagan-Udall Foundation should proceed, with the envisioned funding from Congress. Foundation board membership should be expanded to assure representation from the venture capital community, to gain access to broad knowledge of innovation in the private sector, and to engage smaller companies that are involved in genomics-based diagnostic development.

Recommendation 5. Industry should adopt a proactive and constructive role as FDA seeks to identify and fulfill its regulatory responsibilities related to personalized medicine.

- Industry should respond in a substantive and positive way to RFIs and draft guidance documents, in particular, where appropriate, submitting carefully considered alternative approaches rather than primarily registering objections. In addition, industry should proactively inform FDA of emerging issues where dialogue will be essential to inform policy development.
- To achieve a timely, shared understanding of the hurdles to regulatory approval, test developers should take advantage of existing FDA procedures for consultation in advance of initial regulatory submission.

⁷⁴ New Labeling Information for Warfarin (Marketed as Coumadin), <http://www.fda.gov/cder/drug/infopage/warfarin/default.htm>, accessed August 10, 2008.

⁷⁵ Information for Healthcare Professionals – Abacavir (marketed as Ziagen) and Abacavir-containing medications, <http://www.fda.gov/cder/drug/InfoSheets/HCP/abacavirHCP.htm>, accessed August 9, 2008.

⁷⁶ Herceptin Prescribing Information, revision date May 2008, <http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf>, accessed August 10, 2008.

- For emerging or rapidly evolving technologies with broad application, industry should provide annual projections of the number and type of products in the development pipeline to assist FDA in planning for timely and appropriate policy development and regulatory review.
- Industry should convene trade and professional association meetings to anticipate and alert FDA concerning regulatory issues that are likely to arise with new technological developments.

VII. Coverage and Reimbursement

Background

Regulatory approval of genomics-based, molecular diagnostic products is necessary but not sufficient for the economic viability of such products. Equally important are decisions by government and private insurance payors about whether to accept a new test as eligible for payment (coverage), and if so, how much to pay for it (reimbursement). One might imagine that the relationship between regulatory approval and reimbursement should be simple: regulatory approval certifies that a new product is safe and clinically useful, so payors should, as a matter of course, extend coverage to products that gain regulatory approval. The reality, however, is far more complex.

Health Insurance in the United States

In the United States, payment for health care comes from a variety of sources. In 2005, private insurance accounted for 35% of national health expenditures, Medicare (national health insurance for the elderly and disabled) for 17%, Medicaid (state health insurance for low income individuals and for children) for 16%, individual out-of-pocket expenditures for 13%, other public programs (including the Department of Veterans Affairs, Department of Defense, Indian Health Service, and others) for 13%, and other private sources for 7%.⁷⁷

Each of these categories, in turn, represents a variety of individual payors, each with its own policy with respect to coverage and reimbursement. Private insurance is increasingly dominated by a group of large national and regional managed care organizations. Medicare, which is administered by CMS, encompasses both a traditional fee-for-service insurance plan that continues to be the choice of most beneficiaries, as well as a range of managed care plans. Medicaid is administered at the state level, with each state program having its own coverage and reimbursement policy.

Because of its large beneficiary population and because its rulings are often perceived as setting standards of care, CMS plays an especially important role. However, CMS is concerned only with those innovations that are relevant to the Medicare population, which consists of people aged 65 and older, patients younger than 65 with certain disabilities, and people of all ages with end-stage renal disease. Thus, certain innovations that are of potentially great importance to younger populations may be of limited or no interest to CMS. In addition, for the most part Medicare does not pay for testing and care to prevent disease.

Coverage Decisions

In principle, both public and private payors reimburse for products and services that are judged “reasonable and necessary” in the context of the patient’s condition and medical community standards. Conversely, payors typically refuse to cover products and services that are considered “investigational.” In practice, payors have become increasingly skeptical in assessing innovations and more rigorous in analyzing the relevant evidence. This is especially so when the anticipated economic impact is substantial, when the product or service represents a new class and thus might be viewed both as more challenging to evaluate and as establishing a precedent for future coverage decisions, or when the product or service is viewed as especially controversial.

Marketing approval by the relevant authority (typically FDA) is necessary but may not be sufficient for payors to cover a new product. Payors have several concerns.

⁷⁷ “The Nation’s Health Dollar, Calendar Year 2005: Where It Came From,” exhibit prepared by Center for Medicare and Medicaid Services, accessed September 1, 2008 at <http://www.cms.hhs.gov/NationalHealthExpendData/downloads/PieChartSourcesExpenditures2005.pdf>.

- **Robustness of the Evidence Supporting Safety and Efficacy.** This is a special concern with respect to genomics-based *in vitro* diagnostics. Development of a genomic marker or set of genomic markers as a diagnostic test typically arises from the observation of an apparent correlation between the presence of those markers and the occurrence of some disease state. Without professional training in biostatistics, it is difficult to appreciate the complexity and subtlety of the statistical analyses required to validate such correlations. Factors that complicate the analysis include inherent limitations or quality control issues in the biochemical assays themselves, ambiguities in definition of the disease state, complexities of the underlying physiologic relationships between individual genes and disease states,⁷⁸ and the challenges of finding independent populations and/or biospecimen samples that can be used to rigorously validate a correlation. Because of these complexities, apparent correlations may prove illusory on more rigorous analysis. Payors face the risk that tests that reach the market primarily on the basis of analytical validity and with limited evidence of clinical validity may prove to be ineffective in clinical use. Such tests could consume resources unproductively or even place patients at risk of inappropriate care and/or adverse outcomes.
- **Generalizability of the Evidence Supporting Efficacy and Safety.** Data derived from narrowly defined, tightly controlled study populations in analytic validation studies and clinical trials is not always representative of the results that will be achieved with typical patients in real-world settings. Treatments or diagnostic procedures that seem promising in clinical trials may prove to be less effective in routine practice.
- **Appropriate Use.** Where available evidence does not clearly define criteria for appropriate use, it can be difficult to specify coverage criteria in such a way as to prevent widespread, cost-ineffective use in patients who will not benefit. Diagnostic tests, especially those based on blood samples or on noninvasive imaging, are widely perceived as imposing relatively little risk to a patient as compared to therapeutic interventions. In fact, this is not always true – even a blood draw poses some risk, and false-positive results from diagnostic tests may result in inappropriate treatment or require additional and more-invasive diagnostic tests to clarify the patient’s situation. Payors are concerned that many physicians have a tendency to order diagnostic tests too freely, without sufficient consideration of their necessity and value in managing the patient’s condition.

The consequence of these concerns is that payors want to see more extensive data on diagnostic tests than is required to gain FDA approval in order to validate their benefits in real-world practice settings. For example, as of this writing, neither Aetna nor Cigna covers either the Roche AmpliChip® CYP450 genotyping test or the Invader UGT1A1 molecular assay, despite their marketing approval by FDA. Both payors consider both tests to be, in Aetna’s words, “experimental and investigational because the clinical value...has not been established.”⁷⁹ The gold standard for evidence is considered to be prospective, controlled studies that document not only analytic validity (i.e., that the test measures what it claims to measure) but also improvement in patient outcomes (i.e., increased therapeutic efficacy and/or reduced adverse effects) with the use of a new test. However, payors may also accept indirect evidence – for example, a combination of evidence demonstrating the analytic validity of a test and independent evidence linking the measured biomarker to clinical outcomes – if the overall pattern of such evidence is strong and consistent.

A further complication is that, especially early in the life of a new product or service, coverage decisions may vary by payor and geography. For historical reasons, Medicare uses regional contractors to administer its

⁷⁸ On this point, see “New Findings Challenge Established Views on Human Genome: ENCODE Research Consortium Uncovers Surprises Related to Organization and Function of Human Genetic Blueprint,” accessed July 2, 2007 at <http://www.genome.gov/25521554>.

⁷⁹ Aetna Clinical Policy Bulletin number 0715, Pharmacogenetic Testing, last review 04/25/2008, accessed June 26, 2008 at http://www.aetna.com/cpb/medical/data/700_799/0715.html; CIGNA HealthCare Coverage Position number 0381, Drug Metabolizing Enzyme Genotyping Systems, revised 6/15/2008, accessed June 26, 2008 at http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0381_coveragepositioncriteria_AmpliChip.pdf.

payment process. These contractors also have the primary responsibility for establishing coverage policy through local coverage determination, and regional variations in coverage policy may occur. In certain cases, Medicare deems it appropriate to develop a national coverage determination (NCD). The NCD process can be initiated by CMS analysts or in response to requests received from manufacturers, beneficiaries, or other parties. Private payor policies vary as well. Guidance issued by central technology assessment bodies may be binding or only advisory, depending on the organizational context. Coverage decisions may also vary across insurance products, for example as different companies that sponsor health plans for their employees negotiate different tradeoffs between cost and scope of coverage.

As the text of this report was being finalized, CMS announced that it was considering opening an NCD process for pharmacogenetic testing in 2009,⁸⁰ and opened a public comment period on the topic of pharmacogenomic testing for warfarin response.⁸¹

Reimbursement

Laboratory-based *in vitro* diagnostic tests have traditionally been treated as commodities, to be reimbursed at low and ever-decreasing prices.⁸² The coding systems used to submit claims for reimbursement assume a nearly static world in which most test innovation involves minor changes in well-established methods. Payments for a new test are typically determined in one of two ways. Most commonly, a new test is determined, via a process known as “cross-walking,” to be similar to either an existing test, a mix of existing tests, or a portion of an existing test. Payment will be set at an “appropriate” percentage of the payments for the corresponding existing tests. On occasion, payment is established via “gap-filling,” in which insurers set a price in light of the perceived analytic complexity of a test. Because of the intense focus on analogy to existing tests and on cost as a basis for pricing, “there is little reward for creating additional value (either in a clinical or an economic sense) and hence little incentive to create the evidence to support value creation.”⁸³

Diagnostic tests that are commonly used on an inpatient basis may also be bundled with other products and services under payment systems such as Medicare’s Diagnosis-Related Groups (DRGs). DRGs are designed to incentivize cost-effective provision of hospital care. However, in the short run, before payment rates have been adjusted to reflect changes in technology and practice, DRGs have the effect of pitting emerging technologies against existing approaches in a zero-sum game.

Challenges

Ideally, the reimbursement system should facilitate cost-containment without arbitrarily obstructing the adoption of innovations that deliver substantial value. There are three key challenges to achieving this ideal for genomics-based molecular diagnostics: reimbursement rates, evidence development, and procedural hurdles.

Reimbursement Rates

Reimbursement of genomics-based molecular diagnostic tests as low-margin commodity items radically reduces the likelihood that the economic return from development of an innovative test will justify the required investment.

Evidence Development

The low margins characteristic of reimbursement for *in vitro* diagnostics also make it difficult or impossible to conduct the elaborate clinical trial programs taken for granted in the development of new pharmaceuticals.

⁸⁰ Potential NCD Topics, http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=19, accessed August 10, 2008.

⁸¹ NCA Tracking Sheet for Pharmacogenomic Testing for Warfarin Response (CAG-00400N), <http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=224>, accessed August 10, 2008.

⁸² Wolman DM, Kalfoglu AL, LeRoy L, eds., *Medicare Laboratory Payment Policy: Now and in the Future*, Committee on Medicare Payment Methodology for Clinical Laboratory Services, Institute of Medicine, 2000.

⁸³ Ramsey SD, Veenstra DL, Garrison LP Jr., et al., “Toward Evidence-based Assessment for Coverage and Reimbursement of Laboratory-based Diagnostic and Genetic Tests,” *Am J Manag Care*. 2006 Apr;12(4):197-202.

Even to the extent that funds are available, some companies that are developing innovative molecular diagnostics may be unfamiliar with payors' evidence requirements and may invest available resources less than optimally, designing studies exclusively around the demands of regulatory approval and neglecting the broader evidence required by payors.

Moreover, there is no broad program of government-funded clinical trials of molecular diagnostics comparable to the NIH-funded clinical trials of new therapeutics that complement industry-funded studies and extend the knowledge base in essential ways. More clinical trials such as the TAILORx study of Oncotype DX⁸⁴, coordinated by the Eastern Cooperative Oncology Group and funded by the National Cancer Institute,⁸⁴ and the Genotype Guided Dosing of Warfarin Clinical Trial, coordinated by the University of Pennsylvania and sponsored by the National Heart, Lung and Blood Institute,⁸⁵ are needed. Although systematic reviews such as those conducted by the Evidence-based Practice Centers program⁸⁶ of the Agency for Healthcare Research and Quality (AHRQ) and the Evaluation of Genomic Applications in Practice and Prevention program⁸⁷ of the Centers for Disease Control and Prevention (CDC) play a valuable role, these reviews cannot reach definitive results in the absence of sufficient original data generated by clinical trials. As a result, the evidence base for these new products is frequently inadequate to address the full range of payor questions and concerns.

Procedural Hurdles

Procedural hurdles unrelated to the clinical merits of a product can be substantial barriers to effective market access. Such hurdles include coding systems and bundled payment systems that are not designed to adapt in a timely way to advances in diagnostic technology and complex billing procedures and requirements that obstruct the optimal provision of innovative molecular diagnostics.

Policy Recommendation

Recommendation 6. Public and private payors should determine coverage policies and payment rates for genomics-based molecular diagnostics in light of their overall impact on patient care, as demonstrated by evidence from clinical trials and other well-designed empirical studies.

Reimbursement. Public and private payors should reimburse for molecular diagnostics at levels commensurate with the clinical benefits that these tests provide, as established through well-designed clinical studies. Test developers and payors should collaborate to revise the existing coding system for laboratory diagnostics or establish new, more flexible coding approaches better able to respond to innovation.

Coverage with Evidence Development. Where the available evidence is inadequate to inform coverage and reimbursement decisions, public and private payors should collaborate to expand the use of "coverage with evidence development" programs. In such programs, coverage and reimbursement are extended on a limited basis for use of the product in well-designed studies that will provide evidence on the appropriate use and effectiveness of the product in relevant patient populations.

Standards for Clinical Trial Design. Public and private payors should collaborate in the development of standards for clinical trial designs that would be accepted as providing evidence sufficient for coverage decisions. The major national payors should establish voluntary, formal procedures for consultation with test developers to achieve a timely, shared understanding of what the hurdles for coverage and reimbursement will be in specific cases.

⁸⁴ Understanding PACCT-1: TAILORx, study brochure, Eastern Cooperative Oncology Group, accessed June 26, 2008 at http://ecog.dfci.harvard.edu/general/gendocs/tailorx_brochure.pdf.

⁸⁵ <http://rt5.cceb.med.upenn.edu/warfdcc/WARF-1.html>, accessed June 28, 2008.

⁸⁶ <http://www.ahrq.gov/clinic/epcix.htm>, accessed June 28, 2008.

⁸⁷ <http://www.egapreviews.org/>, accessed June 26, 2008.

VIII. HHS Coordination

Background

As described previously, PCAST considers the primary and most immediate challenges to personalized medicine to be three-fold: research investment in validation of genetic/clinical correlations, restructuring of the regulatory system to effectively accommodate molecular diagnostics, and assuring adequate and appropriate coverage and reimbursement for the resulting products. Primary government responsibility for meeting these challenges, which includes implementing PCAST's recommendations, will lie within a single cabinet-level department, HHS.⁸⁸

HHS agencies play the lead roles in funding biomedical research through NIH, regulating drugs and medical devices through FDA, managing the largest public health insurance program, Medicare, including making decisions on coverage and reimbursement for medical products and services through CMS, and creating and analyzing the evidence base informing appropriate clinical use of new methods of diagnosis and treatment through AHRQ and CDC. In addition, through the ONC, HHS plays a major role in spurring and shaping the development of standards for information technology in health care. Reflecting the centrality of HHS in the implementation of personalized medicine, HHS Secretary Michael Leavitt has made building a strong foundation for personalized health care one of the highest HHS priorities and acknowledges the need for coordination across HHS to accomplish this goal.⁸⁹

Challenges

Under the leadership of Secretary Leavitt and thanks to the extraordinary efforts of Dr. Gregory Downing, program director for the HHS Personalized Health Care Initiative, HHS has made great strides toward defining the scope of personalized medicine activities across and beyond HHS agencies and encouraging a range of information-gathering, standard-setting, and coordination efforts. With these essential efforts as a foundation, HHS faces the challenge of developing a more systematic coordination activity that will be able to sustain the necessary institutional focus over time and across changing administrations.

Coordination is necessary to address several goals. The first goal is to assure, wherever possible, that HHS agencies take adequate account of the impact on personalized medicine when developing and implementing policies to fulfill their respective missions. The second goal is to assure that HHS agencies have the best current scientific and clinical knowledge available when devising policies and activities that relate to personalized medicine. The third goal is to assure that HHS agencies understand the full range of stakeholder perspectives on personalized medicine and its medical, ethical, legal, and social impacts. The fourth goal is to assure that HHS agencies do not work at cross purposes through the issuance of inconsistent guidelines or conflicting regulations. The fifth and final goal is to make the most effective use of limited resources by avoiding duplication of effort and, where appropriate, by implementing initiatives through cross-agency collaboration.

Policy Recommendation

Recommendation 7. HHS should establish a Personalized Medicine Coordination Office (PMCO) within the Office of the HHS Secretary to coordinate all activities relevant to personalized medicine.

The coordination office would be charged with coordination of all HHS activities relative to personalized medicine in order to facilitate progress while ensuring that personalized medicine products meet the highest standards of safety, efficacy, and clinical utility. At the direction of the Secretary, the office would be responsible for identifying

⁸⁸ Other government agencies, such as the Department of Defense, Department of Veterans Affairs, and Department of Energy, may also play a valuable role in related research and/or implementation activities.

⁸⁹ Personalized Health Care: Opportunities, Pathways, Resources, DHHS Report, September 2007.

priority areas for cross-agency coordination and collaboration, managing the necessary cross-agency activities in those areas, and working with affected agencies to implement specific recommendations concerning personalized medicine made by PCAST or other advisory groups.

Important areas for coordination that are related to the research, regulatory, and reimbursement obstacles identified by PCAST as key barriers to progress in personalized medicine include:

- Coordination between NIH and FDA to identify, prioritize, and address challenges in translational research on genomics-based diagnostics that impact both product development and regulation, including many focus areas of the FDA Critical Path Initiative
- Coordination between CMS, FDA, AHRQ, and CDC to assure that the best available data are brought to bear in assessing new personalized medicine products for coverage and reimbursement, without violating necessary strictures on FDA sharing of proprietary information
- Coordination between CMS, AHRQ, and CDC to identify and prioritize gaps in the evidence base concerning outcomes and cost-effectiveness of genomics-based diagnostics and to develop research or consensus-development initiatives to address those gaps
- Coordination between FDA and CMS in rationalizing regulation of laboratory-developed tests
- Coordination between FDA and CMS in educating and consulting with developers of personalized medicine products concerning evidence requirements for reimbursement and regulatory purposes, to facilitate development of more cost-effective clinical trial programs for new products
- Coordination between ONC, FDA, and AHRQ to assure that FDA's regulatory approach to IT-based clinical decision support systems is evidence-based and appropriately targeted

The PMCO would also be responsible for monitoring the progress of personalized medicine and, as new innovations or challenges develop, ensuring that all HHS agencies work together to address emerging needs and take emerging knowledge into account in their respective activities related to personalized medicine.

In that regard, PCAST recommends that the PMCO be responsible for assuring that key areas of policy concern in personalized medicine are brought to the attention of the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS). The PMCO would also be responsible for ensuring that SACGHS findings and recommendations inform HHS policy-making on personalized medicine. Moreover, when the SACGHS charter is reviewed for renewal in September 2008, consideration should be given to adjusting the committee's charter to strengthen its role as an advisor to HHS on the wide range of issues raised by personalized medicine.

Appendix A. PCAST Personalized Medicine Meetings and Presenters

January 9, 2007

PCAST Meeting

- Alex Azar II, U.S. Department of Health and Human Services
- Dr. Raju Kucherlapati, Harvard Medical School-Partners Healthcare Center for Genetics and Genomics
- Dr. Elizabeth Nabel, National Heart, Lung and Blood Institute
- Dr. Janet Warrington, Affymetrix, Inc.

April 24, 2007

PCAST Meeting

- Dr. Elaine Mardis, Washington University
- Michael Goldberg, Mohr Davidow Ventures
- Dr. Randy Scott, Genomic Health, Inc.
- Dr. Jeremy Berg, National Institute of General Medical Sciences

April 25, 2007

PCAST Personalized Medicine Subcommittee Meeting

- Timothy O'Leary, Veterans Health Administration, U.S. Department of Veterans Affairs
- Linda Fischetti, Veterans Health Administration, U.S. Department of Veterans Affairs
- Gail Belles, Veterans Health Administration, U.S. Department of Veterans Affairs
- Dr. Greg Downing, U.S. Department of Health and Human Services
- Dr. Janet Woodcock, U.S. Food and Drug Administration
- John LeGuyader, United States Patent and Trademark Office

July 24, 2007

PCAST Personalized Medicine Subcommittee, Special Meeting

- Vern Norviel, Wilson Sonsini Goodrich & Rosati
- John Barton, Stanford Law School
- Bob Blackburn, DNALex
- Barbara Caulfield, Affymetrix, Inc.
- Larry Respass, Nanogen, Inc.
- Michael Shuster, Fenwick & West LLP
- Dr. Mickey Urdea, Tethys Bioscience, Inc.
- Dr. Michael Hunkapiller, Alloy Ventures, Inc.
- Dr. Richard Janeczko, Luminex Corporation
- Dr. Steve Shak, Genomic Health, Inc.

- Sue Siegel, Mohr Davidow Ventures
- Dr. Bill Young, Monogram Biosciences
- Dr. Howard Birndorf, Nanogen, Inc.
- Dr. Bill Hagstrom, Riley Genomics, Inc.
- Dr. Tom White, Celera Diagnostics
- Brook Byers, KPCB
- Michael Goldberg, Mohr Davidow Ventures
- Dr. Fred Cohen, TPG

September 11, 2007 PCAST Meeting

- Dr. Michael Caldwell, Marshfield Clinic
- Gino Santini, Eli Lilly and Company
- Dr. Mark McClellan, The Brookings Institution
- Dr. Francis Collins, National Human Genome Research Institute

September 12, 2007 PCAST Personalized Medicine Subcommittee Meeting

- Dr. Gregory Downing, U.S. Department of Health and Human Services
- Dr. Gurvaneet Randhawa, Agency for Healthcare Research and Quality
- Dr. Robert Kolodner, U.S. Department of Health and Human Services
- Dr. Barry Straube, Centers for Medicare and Medicaid Services

November 28, 2007 PCAST Personalized Medicine Subcommittee, Special Meeting

- Dr. Nadine Cohen, Johnson and Johnson Pharmaceutical Research and Development, L.L.C.
- Dr. Finley Austin, F. Hoffmann-La Roche Ltd
- Dr. Patrice Milos, Helicos Biosciences Corporation
- Dr. Stephen Teutsch, Merck & Co., Inc.
- Dr. Brian Spear, Abbott Laboratories
- Dr. Hakan Sakul, Pfizer Inc.
- Dr. Jean Paul Gagnon, Sanofi-Aventis U.S. LLC
- Dr. Stephen Ryan, AstraZeneca
- Dr. Myla Lai-Goldman, Laboratory Corporation of America
- David Browning, Phillips Healthcare
- Dr. Joseph Jacobs, Abbott Laboratories
- Dr. John Dunne, BD Biosciences
- Dr. Beryl Crossley, Quest Diagnostics Incorporated

- Dr. Werner Kroll, Novartis Vaccines and Diagnostics, Inc.
- Dr. Walter Koch, Roche Diagnostics
- John Juhasz, Siemens AG
- Dr. Gene Cartwright, General Electric Company
- Nick Littlefield, Foley Hoag LLP
- Gail Javitt, Genetics & Public Policy Center
- Dr. Paul Billings, Signature Genomic Laboratories, LLC
- Dr. John Glaser, Partners Healthcare System, Inc.
- Dr. Mark Hoffman, Cerner Corporation
- Dr. Charles Kennedy, WellPoint, Inc.
- Michael Svinte, IBM Corporation
- Dr. Jonathan Perlin, HCA Inc.
- James Tosone, Pfizer Inc.
- Dr. James Mault, Microsoft
- Rick Carlson, University of Washington
- Dr. Philip Carney, Kaiser Permanente
- Dr. Lewis Sandy, UnitedHealth Group
- Russell Teagarden, Medco Health Solutions, Inc.
- Dr. Bruce Quinn, Electronic Data Systems Corporation
- Dr. Eric Faulkner, RTI Health Solutions
- Dr. Ernst Berndt, Massachusetts Institute of Technology
- Dr. Henry Grabowski, Duke University
- Dr. Tomas Philipson, University of Chicago
- Dr. Kathryn Phillips, University of California, San Francisco
- Mark Trusheim, Massachusetts Institute of Technology

January 8, 2008

PCAST Meeting

- Dr. Ralph Snyderman, Duke University and Proventys, Inc.
- Sharon Terry, Genetic Alliance, Inc.
- Amy DuRoss, Navigenics, Inc.
- Dr. Lawrence Lesko, U.S. Food and Drug Administration

January 9, 2008

PCAST Personalized Medicine Subcommittee Meeting

- Chris Colwell, Biotechnology Industry Organization
- Randy Burkholder, Pharmaceutical Research and Manufacturers of America

- Edward Abrahams, Personalized Medicine Coalition
- Kelly Slone, National Venture Capital Association
- David Mongillo, American Clinical Laboratory Association
- Khaterah Calleja, Advanced Medical Technology Association

April 8, 2008

PCAST Meeting

- Mara Aspinall, Genzyme Corporation
- Dr. Muin Khoury, Centers for Disease Control and Preventio

Appendix B. Examples of Personalized Medicine Applications Currently on the Market

Product	Company	Technology / Test Type	Disease / Application
HER2/neu tests	several	Two types of test are available: immunohistochemical tests measuring expression of the HER2/neu protein (phenotype) and FISH tests measuring amplification of the HER2/neu gene (genotype)	Determine eligibility of breast cancer patients for treatment with Herceptin® (trastuzumab)
Trofile™ assay	Monogram Biosciences	Uses cultured cell lines to assess the interaction of the patient's HIV-1 strain with different cell-surface receptors (phenotype)	Determine eligibility of HIV patients for treatment with Selzentry™ (maraviroc)
TPMT assays	several	Two types of test are available, measuring the presence of TPMT gene variants (genotype) or the level of TPMT enzyme activity (phenotype)	Set dose of thiopurine drugs to maximize therapeutic efficacy while minimizing bone marrow toxicity in diseases such as acute lymphocytic leukemia, inflammatory bowel disease, and severe active rheumatoid arthritis
Invader® UGT1A1 assay	Third Wave Technologies	Uses PCR to measure presence of UGT1A1*28 gene variant (genotype)	Set dose of irinotecan in colorectal cancer patients to maximize therapeutic efficacy while minimizing side effects of diarrhea and reduced white blood cell count
AlloMap® test	XDx	Uses quantitative PCR to measure expression of 20 genes, algorithm to convert results to quantitative composite score (multivariate genotype array)	Identify heart transplant patients at low risk for acute cellular rejection, may allow reduced use of biopsy for monitoring and/or more precise tailoring of immunosuppressive regimen
Oncotype DX®	Genomic Health	Uses quantitative PCR to measure expression of 21 genes, algorithm to convert results to quantitative composite score (multivariate genotype array)	Quantifies the risk of systemic recurrence and assesses the value of chemotherapy in patients with newly diagnosed, early stage invasive breast cancer

Antiretroviral drug resistance tests	many	Wide variety of both genotypic and phenotypic tests commercially available	Assess presence of drug-resistant HIV strains to enable selection of effective antiretroviral regimen
AmpliChip® CYP450 test	Roche Diagnostics	Uses PCR amplification and DNA microarray technologies to assess presence CYP2D6 and CYP2C19 gene variants	Inform dosing decisions for a range of drugs that are metabolized to differing extents by variants of the CYP2D6 or CYP2C19 isoenzymes
Warfarin metabolism tests	many	Variety of kit and laboratory implementations to assess presence of CYP2C9 and VKORC1 gene variants	Inform warfarin dosing decisions in patients requiring anticoagulation therapy
HLA B*5701 test	many LDTs	Generally use PCR amplification and sequence-specific oligonucleotide probes to assess presence of B*5701 allele	Identify HIV patients likely to suffer severe hypersensitivity reaction to the antiretroviral drug abacavir

Appendix C. Technology and Tools Glossary

Base pair: A pair of complementary bases on a double-stranded segment of DNA.

Biobank: See Biospecimen Bank

Biospecimen Bank: A storage repository for biospecimens. Also known as a Biobank.

Biospecimen: A sample of materials such as tissues, cells, nucleic acids, or proteins derived from humans, animals, or plants. Human biospecimens may also be stored with relevant medical information and written consent governing the use of the materials.

Cohort: A group of people that shares a common characteristic or experience within a defined period.

Control: A scientific sample or measurement used as a standard for comparison.

Genetic region: A segment of DNA corresponding to a region of a genome with known or hypothetical genetic activity.

Genetic variation: Variation in the DNA sequence between members of a population or species. Variation may be at the level of changes at a single base pair to changes in whole genetic segments as a result of rearrangement, duplication, or deletion.

Genome annotation: The identification of positions of features such as genes and regulatory elements on a genome sequence.

Genome sequencing: The process of decoding the linear sequence of bases in a segment of DNA.

Genome: An organism's genetic material. The human genome is the DNA contained with the 24 chromosomes, totaling about 3 billion base pairs.

Genome-wide association study (GWAS): A study that identifies markers across genomes to find genetic variation associated with a disease or condition.

Genomics: The study of genomes, including such features as the sequence of bases, the content and locations of genes, regulatory sequences, and nongenic sequences.

Haplotype: A set of variants of closely-linked genetic loci that tend to be inherited together.

HapMap: A map of haplotypes spanning a whole genome.

In vitro diagnostic multivariate index assay (IVDMIA): Test systems that employ data, derived in part from one or more *in vitro* assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition, or is used in the cure, mitigation, treatment, or prevention of disease.

Laboratory-developed test (LDT): Sometimes referred to as "home brew" tests, these tests are assembled by individual clinical laboratories from available reagents and other ingredients for use exclusively in that laboratory.

Longitudinal study: A research study that collects repeated observations of the same items over a long period of time.

Marker: See molecular marker

Microarray: A spotted grid of DNA, protein, or tissue samples attached to a solid support such as a glass slide or silicon wafer permitting simultaneous analysis of all of the samples.



Molecular marker: A native substance such as a protein or DNA sequence associated with a particular physiological state. DNA markers can identify a specific segment of DNA within a larger sample.

Premarket approval (PMA): A regulatory process required for devices that are considered “high risk,” which is defined by the FDA as those that support or sustain human life, are of substantial importance in preventing impairment of health, or which present a potential, unreasonable, risk of illness or injury. A company is required to submit information to the FDA that documents the safety and effectiveness of the device.

Proteome: The entire complement of proteins and associated modifications produced by an organism.

Proteomics: Large-scale studies of protein collections or proteomes with regard to structure and function.

Single nucleotide polymorphism (SNP): DNA sequence variations caused by single base changes at a given position in a genome.

Translational research: The movement of basic scientific discoveries arising from laboratory, clinical, or population studies into clinical applications.

Appendix D. Genomic Technologies

This Appendix provides additional explanatory detail on the technological advances that form the foundation of genomic technologies. For readers interested in more information about the history of the Human Genome Project, the National Human Genome Research Institute has produced an online education kit entitled, “Understanding the Human Genome”⁹⁰ and additional resources related to the history of the Human Genome Project are available through a DOE Web site.⁹¹

The Human Genome Project – a Reference Genome

The human genome sequence announced in 2003 captured the sequences represented by the roughly 20 individuals who provided the DNA samples. This initial composite sequence from a small number of individuals is referred to as a “reference sequence.” A reference sequence is a valuable framework for understanding what is shared among individuals and can form the basis for many discoveries about gene structure and function. However, there is substantial genomic variation within the human population, including single nucleotide variations as well as deletions, insertions, and rearrangements within DNA, which was not captured in the reference sequence. Because this individual variation within the genome influences individual phenotypes, including susceptibility to disease and response to treatment, understanding these phenotypes requires analysis of each person’s own individual genome sequence. For such personal genome sequencing to be performed routinely, new sequencing technologies are needed that are faster and cheaper than those used to establish the reference sequence.

Capturing Genetic Variation

Sequencing of the human reference genome and comparison of the sequence patterns among individuals has made it clear that the genomes of any two individuals are more than 99% identical. However, the small portion that differs is expected to provide insight into individual differences in susceptibility to disease, response to drugs, and reaction to environmental factors. In December 2007, *Science* magazine called human genetic variation the breakthrough of the year⁹² in recognition of the advances made in understanding individual variation in human genome sequences and the impact this will have on elucidating the genetics of complex diseases and traits.

In a collection of individuals, sequence variation may result in several versions – also called “alleles” – of a particular gene, each differing by one or a few nucleotides. Single nucleotide positions in the human genome in which variation exists across many individuals are known as single nucleotide polymorphisms or SNPs, a specific type of allele. SNPs can occur both within and outside of genes, both of which can affect gene function. SNPs occur in the population at frequencies ranging from very common to essentially unique (occurring in a single individual). The relationship between SNP frequency and disease is not currently understood. It has been estimated that approximately 15 million common SNPs exist in human populations.⁹³

SNPs are not the only variation important to understanding disease. Increasingly, the new sequencing technologies as well as array-based techniques are detecting larger variations called “structural variation” or “copy number variation.” These are regions where genomes can differ by large stretches of sequence. For example, a stretch of DNA sequence may be present in one genome but not another (an insertion/deletion); or it may be in a different location or arrangement (rearrangements, inversions). Structural variation can involve stretches of DNA sequence that range in size between a few base pairs to millions of base pairs. Individual (apparently normal) genomes can

⁹⁰ <http://www.genome.gov/25019879>, accessed August 30, 2008.

⁹¹ http://www.ornl.gov/sci/techresources/Human_Genome/project/hgp.shtml, accessed August 30, 2008.

⁹² Pennisi, E. (2007) Breakthrough of the Year: Human Genetic Variation. *Science* 318: 1842-1843.

⁹³ *Science* (2007) 318, 1842-1843.

even differ by the presence or absence of entire genes. Structural variation has also been linked to disease, for example schizophrenia.⁹⁴ Scientists are just beginning to characterize the extent and significance of structural genetic variation.^{95, 96}

Individual genetic variation can be assessed in two basic ways: microarray-based genotyping and genome sequencing. If a set of relevant variants that exist within the human genome are already known (for example, the database of existing, known SNPs), a technique called microarray hybridization today provides a fast, low-cost means of assessing them in an individual's genome. This is known as "genotyping," or assessment of the version (allele) that exists at multiple locations in an individual's genome. Microarrays contain a closely-packed grid of short DNA sequences attached to a solid support such as a silicon wafer. These "chips" can be used to analyze a collection of DNA sequences for allele or SNP variation at specific locations.⁹⁷ Affymetrix, Illumina, and Perlegen market microarray products for this purpose, including arrays containing more than 900,000 SNPs. For example, the Affymetrix GeneChip 500 Mapping Array Set was used in the Wellcome Trust Case Control Consortium genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls published in June 2007.⁹⁸ Manufacturers are now emphasizing inclusion of "tag SNPs," which identify regions of the genome (termed haplotypes), which contain multiple SNPs that are often inherited together, rather than simply increasing the overall number of SNPs represented. New sequence-based approaches to SNP profiling are also commercially available and in development.⁹⁹

Microarrays are also being used for genotyping by companies offering personal genome services.¹⁰⁰ 23andMe, which was founded in 2007, launched its Web-based Personal Genome Service™ in January 2008, genotyping saliva DNA using the Illumina HumanHap550+ BeadChip.¹⁰¹ Navigenics, which was also founded in 2007, genotypes saliva DNA using the Affymetrix Genome-Wide Human SNP Array 6.0® and Clinical Laboratory Improvement Amendments (CLIA) laboratory facilities.¹⁰² A third company, deCODEme, a subsidiary of deCODE Genetics in Iceland, also offers genotyping services in a CLIA laboratory using DNA derived from buccal swabs. deCODEme uses the Illumina Human 1M BeadChip which was developed in collaboration with deCODE Genetics, and contains more than 1 million SNPs per chip.

Although chip-based genotyping is rapid and cheap, it has the significant disadvantage of only detecting variations that are already known to exist in the human population. These are usually variations that exist at relatively high frequency and therefore have been detected by sequencing and placed in a public database so that they can be engineered into the genotyping chips. While such variation may be implicated in a specific disorder, much more commonly the SNP or other variation is simply correlated with a disease state. The actual variation causing the phenotype is in fact just physically nearby the one that can be assayed by genotyping.

In addition to microarray-based genotyping, genome sequencing can detect any variation in an individual, including ones not previously seen and reported. Sequencing can thus be used for discovery of new variations. A complete catalog of human variation that can be used as a basis for the design of all possible genotyping assays has not yet been developed. In addition, we do not yet understand the basis for variation in individual phenotypes such as disease susceptibility. If the most significant diseases or predispositions are caused by rare variants (even rare variants in genes already implicated in disease), sequencing may be the only option for detecting them. As sequencing costs drop, the use of sequencing to obtain more information about an individual's genetic variation

⁹⁴ http://www.nih.gov/news/research_matters/april2008/04072008schizophrenia.htm, accessed August 30, 2008.

⁹⁵ The Human Genome Structural Variation Working Group, Completing the map of human genetic variation. *Nature* 447: 161-165.

⁹⁶ Kidd et al. (2008) Mapping and Sequencing of Structural Variation from Eight Human Genomes. *Nature* 453: 56-64.

⁹⁷ <http://biobasics.gc.ca/english/View.asp?x=737>, accessed August 30, 2008.

⁹⁸ The Wellcome Trust Case Control Consortium (2007) *Nature* 447, 661-678.

⁹⁹ Dove, A (2007) From Morgan to Microarrays: gene mapping hits the big time. *Science* 318, 473-478.

¹⁰⁰ <http://www.nytimes.com/2007/11/17/us/17genome.html>, accessed August 30, 2008.

¹⁰¹ <https://www.23andme.com/more/process/>, accessed August 30, 2008.

¹⁰² <http://www.navigenics.com/>, accessed August 30, 2008.

will be increasingly desirable. If costs drop far enough, whole genome sequencing may supersede microarray-based approaches for assessing genotypes. In the meantime, new variation discoveries afforded by sequencing will continue to feed into the design of new microarrays.

Next Generation Sequencing Technologies/Personal Genomes

The National Human Genome Research Institute Genome Technology Program supports technology development aimed at reducing genome sequencing costs. This program was the result of two concept papers,¹⁰³ discussed at the National Advisory Council for Human Genome Research in May 2003. The initial goal was to sequence a mammal-sized genome (roughly 3 billion base pairs) for \$100,000 but the long-term goal was a genome sequence cost of \$1,000.¹⁰⁴ Beginning in 2004, awards totaling \$99 million¹⁰⁵ were made by the Genome Technology Program¹⁰⁶ to support technology development in both academic and industrial settings, as well as transfer of technologies from developers to users. Sequencing technology advances supported, in part, through this program have led to the development of new sequencing chemistries and the commercial release of several next generation sequencing machines. The 454 Life Sciences Genome Sequencer FLX™,¹⁰⁷ the Illumina Genome Analyzer,¹⁰⁸ the Applied Biosystems SOLiD System™,¹⁰⁹ and the Helicos™ HeliScope Genetic Analysis System¹¹⁰ are already on the market and other sequencing technologies are close to commercialization.

These new sequencing machines represent the first wave of new technologies that could provide rapid access to whole genome sequence information from an individual at low cost. In general, the new sequencing platforms in their initial implementation are between two- and ten-fold more efficient at producing data than the Applied Biosystems 3730xl DNA Analyzer that was used to produce the reference genome sequence. However, the quality of the data is different – for example, the 3730 routinely produced individual sequences (or “reads”) of up to 900 base pairs in length – such long reads can be assembled readily into sequences of many millions of base pairs. The new platforms produce much shorter individual reads – from 35 to 400 base pairs. In addition, variability in sequence quality exists depending on the technology used.¹¹¹ Much work remains to understand how best to exploit this new type of data for all uses.

However, short reads are relatively easy to use for understanding human variation. Because of the availability of a high quality human genome reference sequence as a basis for comparison with an individual genome, it is possible to use the new technology platforms to obtain sequence from an individual genome very efficiently. Less work and shorter reads are required to make the comparison and find individual variation than would be required to sequence an entirely new reference genome for each individual. This is because the short reads can readily be aligned to their proper place using the reference sequence and compared with the reference to detect differences. Decreasing sequencing costs have allowed more ambitious scientific projects to be conceived and undertaken. For example, the National Human Genome Research Institute has initiated two new programs, the Medical Sequencing Program¹¹² and the Tumor Sequencing Project,¹¹³ which are using next-generation machines to sequence targeted regions (chosen because they have been implicated in the disease) of the genomes of many individuals with known conditions. In addition to finding individual variation that can be related to specific disorders, these projects will develop approaches for analyzing the data and managing associated ethical issues.

¹⁰³ http://www.genome.gov/Pages/Education/Sequencing_technology_concepts_for_Council_discussion1.pdf, accessed August 30, 2008.

¹⁰⁴ <http://www.sciencemag.org/cgi/content/full/311/5767/1544>, accessed August 30, 2008.

¹⁰⁵ http://www.genome.gov/Pages/About/OD/ReportsPublications/June2008_SchlossHoL.pdf, accessed August 30, 2008.

¹⁰⁶ <http://www.genome.gov/10000368>, accessed August 30, 2008.

¹⁰⁷ <http://www.454.com/>, accessed August 30, 2008.

¹⁰⁸ <http://www.illumina.com/pages.ilmn?ID=204>, accessed August 30, 2008.

¹⁰⁹ http://marketing.appliedbiosystems.com/mk/get/SOLID_KNOWLEDGE_LANDING, accessed August 30, 2008.

¹¹⁰ <http://www.helicobio.com/Products/HelicostradeGeneticAnalysisSystem/tabid/140/Default.aspx>, accessed August 30, 2008.

¹¹¹ <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1779559>, accessed August 30, 2008.

¹¹² <http://www.genome.gov/15014882>, accessed August 30, 2008.

¹¹³ <http://www.genome.gov/19517442>, accessed August 30, 2008.

The 1,000 Genomes Project – conducted by an international consortium and described in the Technology and Tools chapter of this report – aims to compile a more comprehensive catalog of human variation (seeking rare SNPs and structural variants) for general use in medical genetics studies. This project will test the capabilities of the new platforms even more – one pilot project is testing the ability of the new platforms to sequence all of the genes from over 1,000 individuals, and another aims to test the ability to obtain information about sequence variation over the entire genome of 1,000 individuals. Three sequencing companies, 454 Life Sciences, Applied Biosystems, and Illumina Inc., have joined the project to provide additional sequencing capacity and to test their technologies on hundreds of human DNA samples.¹¹⁴

These technological innovations have already enabled sequencing of the first individual human genomes. As described on page 32 of this report, the sequence of Nobel Laureate James Watson was completed in June 2007 by Baylor College of Medicine in partnership with 454 Life Sciences in two months at a cost of less than \$1 million.¹¹⁵ The sequence was presented to him on a DVD and deposited in a public database. This contrasts with the public Human Genome Project, which cost \$3 billion (including technology development) and took about 13 years. In addition, individuals can now purchase their own genome sequences from Knome, a commercial company (see the Technology and Tools chapter of this report).

Other Applications

Although the most prominent application of sequencing technologies is to understand genomic variation in health and disease, the new technology platforms can be used for other applications that may become increasingly important, and which raise similar ethical, legal, social, and policy issues. Two examples are below.

First, the new platforms can be used to precisely detect changes in the level of expression of all genes that are active in any tissue by sequencing DNA copies made from messenger RNA. As costs decrease, this will be possible to do for individual patients. This will be used for diagnosis and prognosis of disease, and to monitor responses to treatment. Genome-wide expression analysis can also be done using a chip-based approach, but this is rapidly being replaced by next generation sequencing, which is cheaper for this specific application and provides better data quality.

Second, the new sequencing technologies can be adapted to detect epigenetic changes. These are chemical modifications to DNA bases that do not entail actual changes of DNA sequence, but that affect the function of an individual DNA sequence by changing the structure of the DNA, and/or by changing how proteins bind to DNA. Epigenetic changes are known to be important for normal development and disease. There are several efforts underway to catalog human epigenetic variation and epigenomics was one of two new NIH Roadmap Initiatives for 2008.¹¹⁶

The Future

Both sequencing and microarray technologies are changing rapidly and will continue to do so over the next few years. For detecting known variation, genotyping assays now cost on the order of \$1,000. As more basic knowledge is built up about the relationship between genome sequence and disease, genotyping approaches will become more powerful and increasingly used in routine medical settings to determine patient predispositions to disease and response to drug treatment. Even so, because of its capacity to uncover all variation, sequencing will always be the last word in understanding individual variation.

The \$1,000 genome sequence is not yet a reality but appears to be increasingly feasible within the next 10 years. The current “next generation” technologies will probably enable sequencing of a whole human genome at a cost of less than \$100,000 within the next three years. The next step in the evolution of new sequencing technologies will

¹¹⁴ http://www.1000genomes.org/bcms/1000_genomes/Documents/Sequencing%20Companies%20Join%201000%20Genome%20Project.pdf, accessed August 30, 2008.

¹¹⁵ http://www.bcm.edu/news/packages/watson_genome.cfm, accessed August 30, 2008.

¹¹⁶ Pennisi, E. (2008) Are Epigeneticists Ready for Big Science? *Science* 319: 1177.

likely allow sequencing of long, continuous, stretches of single DNA molecules, overcoming the limitations of short “reads,” and improving data quality.

As sequencing costs decrease, it will be possible to contemplate new types of clinical application and basic research of direct relevance to human health. The ability to address new types of research question is likely to enable rapid advance of the entire biomedical research enterprise. For example, the Human Microbiome Project seeks to understand the many billions of bacteria and other microorganisms that live in or on healthy humans, and which are known to have an effect on our health. A complete understanding of these microbes requires sequencing their genomes (it is the only way we know to even detect their presence), which cannot be done without abundant, cheap sequencing capacity. As the technologies move forward, we will increasingly be able to detect and understand all changes in our DNA, including those occurring during development, during aging, as a result of environmental exposures, and as a cause or result of disease processes.