Stakeholder Engagement Workshop

February 25, 2015

Bethesda, Maryland

Revised May 7, 2015

This meeting summary was prepared by Samuel Thomas, Rose Li and Associates, Inc., under contract to the National Institutes of Health (Contract number HHSN271201400038C). The views expressed in this document reflect the opinions of the meeting participants and not necessarily those of the National Institutes of Health, the U.S. Department of Health and Human Services, or any other organizations with which participants are affiliated. Review of earlier versions of this meeting summary by the following individuals is gratefully acknowledged: Naomi Aronson, Gregory Bloss, Bruce Blumberg, Sarah Duffy, John Haaga, Daniel Hayes, Mitchell Higashi, Chandra Keller-Allen, Allison Kurian, Rose Maria Li, Teri Manolio, Diego Ossa, Bray Patrick-Lake, Josh Peterson, Gurvaneet Randhawa, Marc S. Williams, and David Veenstra.

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Acronym Definitions

Acronym	Definition
AHRQ	Agency for Healthcare Research and Quality
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BCBSA	Blue Cross and Blue Shield Association
BRCA	breast cancer susceptibility gene
CDER	Center for Drug Evaluation and Research
CISNET	Cancer Intervention and Surveillance Modeling Network
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare & Medicaid Services
CTTI	Clinical Trials Transformation Initiative
EGFR	epidermal growth factor receptor
EHR	electronic health record
FDA	Food and Drug Administration
IL28B	interleukin 28B
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCCS	National Coalition for Cancer Survivorship
NHGRI	National Human Genome Research Institute
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
PMI	Precision Medicine Initiative
PREDICT	Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment
PriMER	Personalized Medicine Economics Research
RIGHT	Rational Integration of Genomic Healthcare Technology
USPSTF	U.S. Preventive Services Task Force
VOI	value-of-information

Executive Summary

On February 25, 2015, the National Institutes of Health (NIH) Health Economics Common Fund Program convened a workshop to engage a range of stakeholders in discussions about how NIH-funded research can enhance the role of personalized medicine in improving the efficiency and effectiveness of health care.[1] The goal of the workshop was to facilitate dialogue among researchers, stakeholders, and NIH staff to (1) inform stakeholders of ongoing NIH-funded research initiatives and (2) help researchers focus on questions of critical value to stakeholders.

Participants included invited panelists representing diverse stakeholder groups, investigators leading cooperative agreements funded under the auspices of the Common Fund program on *Determinants and Consequences of Personalized Health Care and Prevention*,[2] and NIH staff. The invited panelists represented five broad stakeholder groups: (1) health care providers, (2) patient advocates, (3) guidelines organizations, (4) insurers, payers, and health technology assessment organizations, and (5) pharmaceutical and diagnostic developers, manufacturers, and regulators.

The workshop began with brief presentations summarizing the ongoing cooperative agreement research projects. Each project seeks to understand and identify strategies to maximize the potential value of genomic technology and other personalized medicine approaches. The projects utilize analyses of large data sets, multiple modeling and simulation techniques, cost-effectiveness and value-of-information analyses, and/or surveys to achieve their aims. The project investigators expressed a desire to produce tools and information that are useful to stakeholders. Panel presentations and discussions followed, during which each invited panelist shared his or her perspective on the research and clinical practice needs of the field. An overview of the recently launched Precision Medicine Initiative (PMI) was also included in the agenda.

Health Care Providers

The first panel highlighted the perspectives of health care providers. A major theme was the challenge posed by the rapid growth in genomic testing to clinical decision making at both the provider and system levels.

- Although genomic tests have great potential to inform diagnoses and treatment decisions, many tests currently lack evidence to clearly support clinical decisions.
- There are outstanding research needs as well as a need to educate both patients and providers about appropriate interpretation of genomic data and genetic risk factors of disease.

[1] More information about the Health Economics Common Fund Program is available at https://commonfund.nih.gov/Healtheconomics/.
[2] The funding opportunity announcement is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-12-024.html.

- The panelists also discussed a systems-level tension between the desire to keep up with the pace of technological development and the need to base decisions on sound evidence, which takes time to produce.
- New economic tools are required to support pragmatic decision making in an evidence-poor environment.

Patient Advocates

The second panel elicited insights from patient advocates on the importance of personalized medicine from the patient perspective.

- Patients have diverse preferences that influence their health care choices, including heterogeneous perceptions of risk and anxiety and different definitions of quality of life.
- Truly personalized medicine will consider these types of individual preferences.
- Patients have a hunger for information, and there is a need for greater education about risk and the distinction between clinically useful information and data that are not clinically useful or meaningful.
- Participants noted a potential tension between the preferences of individual patients and optimizing public health.

Guidelines

The third panel comprised representatives of organizations that issue formal clinical guidelines and recommendations.

- Clinical guidelines are beginning to incorporate aspects of personalized medicine, especially genomic tests and biomarkers, as the evidence base for clinical use grows.
- Participants agreed that information on cost-effectiveness could affect guidelines, provided the information is current, reliable, reproducible, and efficiently produced.

Payers

The fourth panel considered how payers view the challenges and opportunities posed by personalized medicine. Panelists included representatives of both government and private payers. There are substantial differences between public and private payment systems in the factors affecting their coverage decisions. Public payments are determined by statutes and regulations, whereas evidence of clinical utility is the primary criterion for coverage by private insurers.

- As new personalized medicine tests and clinical evidence emerge, payers and providers will need new tools to manage, interpret, and make decisions based on a plethora of new information.
- New incentives will also be needed to better align practice with emerging evidence.

Industry

The final panel presented perspectives from representatives of the pharmaceutical and diagnostic industries and of the Food and Drug Administration (FDA). The presentations

identified two significant challenges facing the development of new personalized medicines: knowledge gaps in basic science and misaligned economic incentives for innovation. Regulatory approval of new treatments and diagnostics depends on the existence of sound evidence.

- Although the FDA has demonstrated an ability to quickly approve molecularly targeted therapies, targeted therapies are dependent on how well the science is understood—in particular the molecular and genetic causes and pathways of the disease.
- Panelists noted that the current pricing and reimbursement landscape poorly incentivizes industry to develop new personalized medicine technologies.
- Value-based pricing schemes and combined reimbursements for treatments and companion diagnostics would help promote innovation.

The workshop concluded with a summary discussion in which participants reflected on the themes raised throughout the meeting and suggested possible paths forward. In order to increase the relevance of research on the economics of personalized medicine for decision makers, participants suggested the following:

- Generate evidence on the use and impact of precision medicine technologies to inform economic assessments
- Prioritize research investments to generate evidence
- Present research results and cost-effectiveness measures in multiple formats
- Develop transparent models that stakeholders could adjust to their needs
- Encourage communication between the research and health care delivery communities

Workshop Summary

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The workshop was organized in two parts. First, the investigators leading the cooperative agreement projects presented brief overviews of their research. Panel presentations followed, during which each invited panelist shared his or her perspective on the research and clinical practice needs of the field. Each panel concluded with a discussion moderated by one of the cooperative agreement investigators. The workshop also featured an overview of the recently launched Precision Medicine Initiative (PMI).

This document summarizes the workshop proceedings, focusing on the panel presentations and discussions. The workshop agenda and list of participants are appended.

Introduction

Gregory Bloss and Scott Ramsey welcomed the participants and explained the background and goals of the workshop. Bloss noted that the discussions are intended to elicit the full range of perspectives and opinions among invitees rather than to achieve consensus or to draft recommendations. Ramsey added that opinions expressed during the workshop will inform the current cooperative agreement research projects. Finally, it is hoped that the workshop discussions will lead to new collaborations among the attendees.

[3] More information about the Health Economics Common Fund Program is available at https://commonfund.nih.gov/Healtheconomics/.
[4] The funding opportunity announcement is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-12-024.html.

Cooperative Agreement Projects

Rational Integration of Genomic Healthcare Technology

Josh Peterson, Vanderbilt University Medical Center

Panel-based genotyping and sequencing are increasingly common, yet the value of preemptively genotyping large populations is unknown. The Rational Integration of Genomic Healthcare Technology (RIGHT) project is a modeling and simulation study that explores the potential return on investment and patient impacts of the Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment (PREDICT) program, which implements broad preemptive genotyping of patients using a multiplex panel. Specifically, RIGHT aims to (1) design strategies for selecting high-yield patient populations for preemptive genotyping, (2) compare the cost-effectiveness of several genotyping strategies, and (3) perform value-of-information (VOI) analyses to determine the economic value of system features, including provider behavior.

RIGHT employs a discrete event simulation model with three components: a predictive submodel to select patient populations for genotyping, an indication submodel to simulate the rate at which patients develop drug indications over time, and an outcome assessment submodel to compare outcomes among genotyped and non-genotyped populations. Preliminary results suggest that there are fewer clinical events in the preemptively genotyped populations, and that a difference of relatively few events can offset the upfront costs of preemptive genotyping. Future efforts will include creating a more general simulation framework that can be used on any panel of genes, using different types of risk scores, simulating multiple simultaneous pharmacogenomics risks, and examining the impact of variable prescriber behavior. Ultimately, the investigators hope to inform the design of umbrella trials that could use the framework to determine statistical power and which patient populations to enroll.

Value of Personalized Risk Information

David Kent and Peter Neumann, Tufts Medical Center

Heterogeneous patient characteristics lead to variation in outcome risk and, therefore, treatment benefits. Averaging results across heterogeneous patients can therefore be misleading if applied to an individual patient. Moreover, conventional subgroup analyses that examine one variable at a time often inadequately detect differences in treatment effects across different groups of patients and are prone to false positive correlations in part because multiple variables sometimes vary together. A better approach is to use risk models that assess multiple variables simultaneously and aggregate patients into subgroups that are likely to have clinically meaningful differences in their treatment effect.

In this context, the present project aims to (1) examine the value of a risk-based approach to individualized care and cost-effectiveness across a range of medical interventions, (2) develop and test methods to assess prediction models, and (3) explore the policy implications of using a

risk-based approach to individualize care by simulating the impact of incentive-based programs, such as tiered insurance plans, and engaging stakeholders on real-world implementation.

Personalized Medicine Economics Research (PriMER)

Anirban Basu, Josh Carlson, and David Veenstra, University of Washington

The goal of this project is to achieve a better understanding of the factors that influence different stakeholders' adoption of genomic technologies. The specific aims are (1) to develop an economic model for prioritizing personalized medicine research and evaluating specific technologies; (2) to assess patient, provider, and payer preferences for personalized medicine; and (3) to create a pragmatic decision framework to address evidence uncertainty in personalized medicine and inform clinical guideline and reimbursement policies.

The first aim will build on the previously developed model of expected value of individualized care to quantify the value of information for decision making. The assumptions of the baseline model will be systematically relaxed to account for uncertainty and variation in adoption and real-world use of personalized medicine tests. The second aim will involve qualitative and quantitative interviews with a range of stakeholders to identify and estimate the importance of factors driving the adoption of personalized medicine technologies. This will inform the aforementioned model and allow predictions of the probability of adoption of specific technologies. Finally, the third aim will employ VOI analyses to assess the monetary value of conducting future research on specific personalized medicine technologies. The results of these studies will be used to develop a pragmatic framework to assist guidelines organizations and payers making decisions in the context of evidence uncertainty.

Optimizing Personalized Care Using Economic Studies of Cancer Genomic Testing

Tracy Lieu, Kaiser Permanente Northern California, Jeanne Mandelblatt, Georgetown University, and Scott Ramsey, Fred Hutchinson Cancer Research Center

A growing number of genomic applications are being developed for cancer. Most of these are used to inform treatment choices, and many are marketed directly to consumers. For example, the Onco*type* DX® Breast Cancer Assay measures the expression of 21 genes and provides a risk score for distant recurrence. Although the test has had some clinical impact in reducing harms caused by unnecessary chemotherapy, its developer, Genomic Health, funded the majority of published studies. Use of Onco*type* DX® is expanding to new indications despite a paucity of evidence.

The present study aims are to (1) identify factors that influence the cost-effectiveness of genomic testing, including Onco*type* DX®, in community practice; (2) retrospectively analyze patterns of care from electronic records of more than 13,000 breast cancer patients eligible for genomic tests in two regions, and survey a nested sample of patients and providers to identify influential factors used in decisions around genomic tests; and (3) integrate cohort and survey data into a Cancer Intervention and Surveillance Modeling Network (CISNET) simulation model

to evaluate cost-effectiveness based on actual community practice, and evaluate how multi-criteria decision analysis compares with traditional cost-effectiveness analysis.

Precision Medicine Initiative at NIH

Teri Manolio, National Human Genome Research Institute (NHGRI)

President Barack Obama announced the launch of a new Precision Medicine Initiative (PMI) during his 2015 State of the Union address. Over the past decade, key advances that will enable the PMI have occurred in genomics, electronic health records (EHRs), mobile health technologies, data science, and patient partnerships. The PMI will include three primary components:[5]

- **Near Term:** Cancer as a model for precision medicine
- **Longer Term:** Expanding the model to other diseases
- **Policy Changes:** Remove barriers to clinical implementation

NIH held a workshop on February 11-12, 2015, to discuss the longer-term effort for expanding precision medicine to diseases beyond cancer.[6] The vision is to create a national research cohort of more than 1 million volunteers to generate a knowledge base for precision medicine. Participants would share genomic data, lifestyle information, and biological samples—all linked via EHR. The goal is to provide a ready platform for new studies and to engage participants as research partners. Other topics discussed at the PMI workshop included participant recruitment, data privacy, mobile data collection, informatics, and possible use cases for the cohort. The next steps will be to form a Working Group that will report to the Advisory Committee to the Director, collect further information, and begin drafting a plan.

Stakeholder Panels

Invited panelists presented their perspectives on the most critical research needs and challenges facing personalized medicine. Each panel concluded with a discussion moderated by one of the cooperative agreement investigators. *The following summaries of panelist presentations reflect the views of the individual presenter and not necessarily the view of the organizations with which they are affiliated.*

PANEL 1: HEALTH CARE PROVIDERS

Next-generation Sequencing for Cancer Risk Assessment: Progress and Challenges

Allison Kurian, Stanford University

Rapid progress has been made in genetic technology, and whole genomes may now be sequenced for about $1,000. In the clinic, multi-gene panels of up to 200 genes are replacing single-gene tests. More patients are now being tested for more genes than ever before; yet

[5] Information about the PMI is available at http://nih.gov/precisionmedicine/.
[6] Information about the workshop is available at http://www.nih.gov/precisionmedicine/workshop.htm.

how clinicians should translate genetic data into effective patient care is not always clear because the relevant genetic pathways are numerous and complex.

Hereditary risk breast cancer is a prominent example. The breast cancer susceptibility genes (*BRCA1* and *2*) were discovered in the mid-1990s. An influx of patients requesting genetic testing was observed following the 2013 publication of an opinion article in *The New York Times* by Angelina Jolie, a celebrity who underwent a prophylactic double-mastectomy after learning she was *BRCA1* positive. Shortly thereafter, the U.S. Supreme Court ruled against patenting of genetic tests. This spurred competition and reduced costs. Genetic panel tests for breast cancer now cost about $1,500 and are often covered by insurance. The major cost is the interpretation of sequencing data. Genetics expertise is essential for both deciding which tests to order and for interpreting results of uncertain clinical significance.

In a recent study, Kurian and colleagues found that 10 percent of women with breast cancer who underwent genetic panel testing had a potentially actionable mutation and 88 percent had at least one genetic variation of unknown significance.[7] All study patients requested their test results. The care of some patients was altered based on the genetic test results.

There are several outstanding questions about the clinical utility of multi-gene panel tests:[8] How much does cancer risk vary, and can low- and high-risk mutation carriers be identified? Can strategies for familiar genes be extrapolated for emerging genes? Do patients want more genes tested? Can they understand the test results and tolerate the uncertainties? How should patients' relatives be counseled? How do panel tests affect treatment, prevention, and survival? Are invasive prevention strategies such as mastectomy overused?

Challenges in Establishing and Evaluating the Clinical Value of a Genetic/Genomic Test: Kaiser Permanente's Approach(es)

Bruce Blumberg, Kaiser Permanente Northern California

Kaiser Permanente is an integrated health system, serving as both the payer and provider for 9.6 million patients. As such, Kaiser provides both individual- and population-level care. Foundational elements of Kaiser's integration include its scale, EHRs, group practice setup, and internalization. Among its principles of practice is the responsible stewardship of salaried physicians.

Blumberg discussed the key questions clinicians ask when deciding whether to order a test for a particular patient. The most important question is whether the test results will influence the management of patient care. For example, a test could inform the choice of therapies,

[7] Kurian, Allison W., Emily E. Hare, Meredith A. Mills, Kerry E. Kingham, Lisa McPherson, Alice S. Whittemore, Valerie McGuire, et al. "Clinical Evaluation of a Multiple-Gene Sequencing Panel for Hereditary Cancer Risk Assessment." *Journal of Clinical Oncology* 32, no. 19 (July 1, 2014): 2001–9. doi:10.1200/JCO.2013.53.6607.
[8] Kurian, Allison W., James M. Ford. "Multigene Panel Testing in Oncology: How Should We Respond?" *JAMA Oncology*, published online March 5, 2015. doi:10.1001/jamaoncol.2015.28.

surveillance regimens, or prognosis. It could also help avoid invasive or expensive tests or procedures. Other relevant questions include whether there are published guidance documents, effective alternatives, risks of testing, regulatory considerations, or conflicts of interest.

The key questions clinicians ask when deciding whether to implement a screening program are somewhat different. Implementation costs and strategies, opportunity costs, and the educational needs of the public and providers must be considered. Additional concerns about equity among diverse populations must also be addressed. To make informed decisions, there is an outstanding need for genomics education and for studies that demonstrate benefits in terms of health outcomes.

Economic Analysis in Genomics: Focus on Perspective

Marc S. Williams, Geisinger Health System

Although his presentation focused on genomics, Williams provided a more inclusive definition of personalized medicine: "the practice of clinical decision making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual's state as is available."[9]

Most economic analyses are performed from a societal perspective. This perspective translates poorly to decision making at the health system level. Economic tools must be adapted for use in different settings. Williams shared three examples of such adaptations: a health systems perspective of universal screening for Lynch syndrome, a hypothetical analysis of interleukin 28B (*IL28B*) testing to facilitate future decision making, and a patient perspective on pharmacogenomics testing to inform warfarin dosing.

A model was used to compare different screening strategies based on the average cost per case detected in order to evaluate strategies for universal screening for Lynch syndrome of colorectal cancer patients within a health system context.[10] The model has proved useful for practical decision making and was subsequently used to demonstrate that limiting screening to high-risk age groups would miss half of all cases. The model has also been applied to endometrial cancer.

Although economic analyses support the cost-effectiveness of triple therapy with protease inhibitors for hepatitis C viral genotype 1, dual therapy without protease inhibitors remains the standard treatment for viral genotypes 2 and 3. Williams and colleagues wondered whether patient *IL28B* genotype, which predicts response to treatment in all hepatitis C viral genotypes,

[9] Pauker, Stephen G., and Jerome P. Kassirer. "Decision Analysis." *New England Journal of Medicine* 316, no. 5 (January 29, 1987): 250–58. doi:10.1056/NEJM198701293160505.

[10] Gudgeon, James M., Janet L. Williams, Randall W. Burt, Wade S. Samowitz, Gregory L. Snow, and Marc S. Williams. "Lynch Syndrome Screening Implementation: Business Analysis by a Healthcare System." *The American Journal of Managed Care* 17, no. 8 (2011): e288–300.

could be used to select candidates with viral genotypes 2 and 3 for triple therapy and, if so, how much improvement in sustained viral response would be needed to achieve cost-effectiveness of screening.[11] They found that administering triple therapy to patients with the resistant *IL28B* genotype required an improvement in sustained viral response of only 2 percent to be cost-effective. In contrast, treating all patients would require a response improvement of 11 percent.

A third example highlighted the importance of a patient-centered perspective. An analysis of the cost-effectiveness of using pharmacogenomic testing to inform warfarin dosing found little difference in cost-effectiveness between testing versus no testing.[12] Based on prospective trial data, however, patients who received pharmacogenomic testing required significantly fewer laboratory blood tests. In the context of equivalent costs, a patient-centered perspective would favor the pharmacogenomic testing approach based on reduced patient burden.

These examples highlight the importance of defining analytical perspective and demonstrate that economic tools can be used to pragmatically rationalize decision making. A significant challenge is the lack of publication outlets for economic studies that adapt methodological approaches to better meet the needs of decision makers.

Discussion

Moderator: Tracy Lieu, Kaiser Permanente Northern California

The panelists discussed how health care systems are coping with the increasing abundance of genetic data, which in many cases lack evidence to clearly support clinical decisions. Clinical guidelines have recently begun incorporating multiplex panel testing, and there is significant regional variation in utilization of these tests. In some health systems, such as Kaiser Permanente, genomic tests that produce both clinically useful and extraneous data are part of standard practice. Although it is clear how clinicians should respond to the small percentage of actionable findings, the meaning of many incidental findings is ambiguous. Blumberg remarked that relying on genetics counseling programs is not a sustainable long-term solution because eventually physicians will need to learn to act independently based on the results of genomic tests.

Geisinger Health System and Regeneron recently formed a large-scale exome sequencing collaboration. Preliminary results suggest that, when strict criteria are applied, only 2 to 3 percent of patients have clinically actionable findings. Yet Williams noted that strict criteria are

[11] Bock, Jonathan A., Kimberly J. Fairley, Robert E. Smith, Daniel D. Maeng, James M. Pitcavage, Nicholas A. Inverso, and Marc S. Williams. "Cost-Effectiveness of IL28B Genotype-Guided Protease Inhibitor Triple Therapy versus Standard of Care Treatment in Patients with Hepatitis C Genotypes 2 or 3 Infection." *Public Health Genomics* 17, no. 5–6 (2014): 306–19. doi:10.1159/000365939.

[12] Meckley, Lisa M., James M. Gudgeon, Jeffrey L. Anderson, Marc S. Williams, and David L. Veenstra. "A Policy Model to Evaluate the Benefits, Risks and Costs of Warfarin Pharmacogenomic Testing." *PharmacoEconomics* 28, no. 1 (2010): 61–74. doi:10.2165/11318240-000000000-00000.

often not used. Instead, laboratories report more findings than are necessary, possibly to reduce their liability and shift decision making to providers. Some pharmacogenomic findings that inform optimal dosing are more relevant for pharmacologists than physicians; test results should be disseminated to relevant providers accordingly.

Several companies (e.g., 23andMe) now offer patients access to genomic testing outside of the health care system. Other companies (e.g., Genetic Genie) offer interpretation of genomic data produced by these tests, including methylation and detoxification profiles. Such independent services are becoming popular despite the great ambiguity of interpreting results.

Daniel Hayes advocated regulating genomic tests based on their clinical utility and with similar scrutiny to regulation of therapeutics. In the current regulatory environment, any company can market a biomarker test and consumers will not know whether the results are analytically or clinically valid. Williams noted that payers are the default regulators because they determine which tests are reimbursed, thereby influencing adoption.

A tension was observed between the need for health care systems to be nimble enough to keep up with the pace of technological development and the need to base health care decisions on sound evidence, which takes time to produce. Tools are needed to support clinical decision making in an evidence-poor environment. Modeling techniques such as sensitivity analysis can help determine the most critical parameters for which more evidence is needed.

PANEL 2: PATIENT ADVOCATES

Remarks on Patient Perspectives

Bray Patrick-Lake, Clinical Trials Transformation Initiative

Patients want a health care system that enables reliable and timely access to prevention and treatment options that are effective, evidence-based, and responsive to the needs and characteristics of individual patients. At present, heterogeneity of treatment effects and a poor understanding of differences by subgroups obscure prediction of individual outcomes. Finite resources are thus wasted on treating patients who will not benefit while, at the same time, other patients experience avoidable adverse events. Instead of waiting for personalized medicine research to catch up, patients are seeking genetic information and interpreting complex results themselves, without health care consultations.

The patient community recognizes that the translational research cycle exists within a larger learning continuum with both linear and cyclical elements. Patients hope that each iteration of the research cycle results in increased scientific understanding, improved outcomes, and decreased medical costs. Advancement depends on successful implementation and diffusion. Finally, patient groups are interested in carefully investing their limited resources in research with greatest potential for improving the most patients' lives.

Remarks on Patient Perspectives

Shelley Fuld Nasso, National Coalition for Cancer Survivorship (NCCS)

Patients must be better educated about risk. At the same time, researchers must consider patient perceptions of risk, including the impacts of fear and anxiety. Even when evidence does not indicate a particular treatment (e.g., prophylactic mastectomy), it may confer significant psychological benefits to certain patients. Patient perceptions of risk may also evolve over the course of an illness. Similarly, harms are not equal to all patients, and individuals define quality of life differently. Not having to travel to the clinic for a test or procedure may itself be a significant benefit. Truly personalized medicine will consider these types of individual preferences and use them to inform treatment recommendations.

Molecular tests marketed directly to consumers—and even to physicians—are appealing, but often provide abundant data that are not actionable. Patients often lack appropriate guidance and counseling even when the information is potentially actionable. Patients are concerned about the accuracy and clinical validity of tests. Given these concerns, the NCCS supports the Food and Drug Administration's (FDA) effort to regulate laboratory-developed diagnostic tests.

Discussion

Moderator: Anirban Basu, University of Washington

Patients have diverse preferences that influence their health care choices. For example, anxiety or other psychosocial concerns may drive patients to choose aggressive treatments even when those treatments are not supported by evidence. Several investigators acknowledged the importance and the challenges of incorporating patient preferences such as anxiety into cost-effectiveness models.

Another preference shared by many patients is a desire for information. When patients cannot obtain information from their health care providers, they will seek it on the internet. One problem is that patients (and providers) often confuse data and information. For example, a gene of unknown significance is data, but it is not information. Sometimes accumulating data in the search for information produces useful results, and sometimes it does not. Providers can play a role in educating patients on the distinction between data and information.

There is a potential for tension between the preferences of individual patients and optimal decisions for public health. For example, an individual patient may wish to receive a given treatment regardless of its cost or evidence base, but if all patients behaved this way the societal costs might be unsustainable and public health outcomes might be suboptimal. Patrick-Lake noted that patient advocacy groups aim to maximize population-level benefits and might be effective partners with providers in educating patients about risk-benefit analysis. Engaging more patients across the continuum of clinical research—not just in a transactional manner—may also help change perspectives.

PANEL 3: PERSPECTIVES ON FORMAL GUIDELINES

National Comprehensive Cancer Network Guidelines

Robert Carlson, National Comprehensive Cancer Network

The NCCN is an alliance of 25 academic cancer centers working to improve the quality, effectiveness, and efficiency of cancer care. Guidelines are the NCCN's core product, and NCCN Clinical Practice Guidelines set the standard for clinical care throughout the United States and form the basis for many insurance coverage decisions and quality evaluations. NCCN guidelines are available online.

NCCN guidelines are developed through an explicit process by multidisciplinary expert panels that include patient advocates as full members. An evidence-based approach is used whenever possible. Evidence, however, is often unavailable. Thus, NCCN identifies the level of evidence on which every guideline is based. The categories of evidence and consensus are as follows:

> **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
>
> **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus (at least 85 percent) that the intervention is appropriate.
>
> **Category 2B:** Based upon lower-level evidence, there is NCCN consensus (between 50 and 85 percent) that the intervention is appropriate.
>
> **Category 3:** Based upon any level of evidence, there is major NCCN disagreement (at least three institutions on each side) that the intervention is appropriate.

NCCN issues guidelines across the continuum of care from risk assessment to end-of-life care. Although high-level evidence is available in certain areas of the continuum, there are gaps. Expert consensus fills the gaps. Only about 6 percent of recommendations are based on high-level evidence. This is not a deficiency of the guidelines, but of the data.

Block scoring graphics accompany written guidelines to visually communicate the level of the efficacy, toxicity, quality/quantity of evidence, consistency of evidence, and cost on a consistent five-point scale. For each measure, more shaded boxes indicate more favorable conditions (i.e., toxicity and cost are displayed on an inverse scale).

More than 800 biomarkers are recommended throughout the guidelines. NCCN publishes a separate biomarker compendium, in tabular form, that helps payers and other stakeholders understand which biomarkers are endorsed by the NCCN and for what purpose. Only biomarkers that inform clinical decision making, and not those used exclusively for research purposes, are included. Clinical uses of biomarkers include screening, diagnosing, monitoring, and providing predictive or prognostic information. NCCN guidelines specify which biomarkers should be measured, but not how to measure them.

Perspectives on Formal Guidelines

Daniel Hayes, American Society of Clinical Oncology (ASCO)

Hayes defined personalized medicine as getting the right drug to the right patient at the right time, dose, and schedule and noted that it requires accurate and reliable diagnostics. For cancer, tumor biomarker tests are particularly important for risk assessment, screening, prognosis, prediction of therapeutic effect, and monitoring.

ASCO issued its first guidelines on hematopoietic colony-stimulating factors and tumor markers in 1994 and 1996, respectively. ASCO guidelines complement NCCN guidelines: NCCN guidelines are horizontal (i.e., each outlines a treatment pathway for a given patient with a disease), whereas ASCO guidelines are vertical (i.e., each is an in-depth exploration of a selected topic).

ASCO's guidelines for breast cancer tumor biomarkers address five categories of tests in specific clinical settings. The guidelines are conservative and only recommend evidence-based biomarkers that would change clinical decisions. Most commercial tumor marker assays are analytically valid (i.e., they accurately and reliably measure what they claim) but are not clinically useful (i.e., their results would not change clinical decisions in a way that evidence shows would improve outcomes). Yet a poor biomarker can be as harmful as a bad drug.

Hayes and colleagues examined factors contributing to the scarcity of tumor biomarker tests with both analytical validity and clinical utility.[13] They describe the existence of a vicious cycle wherein a weak regulatory environment and poor reimbursement structure lead to low investment in tumor biomarkers. This, in turn, produces poor quality evidence, higher scrutiny and skepticism, and few recommendations for clinical use. Biomarkers are thus poorly valued, thereby starting the cycle anew. Hayes and colleagues offered several recommendations to break the cycle, including regulatory reforms, reimbursements commensurate with value, and increased funding for biomarker research.

Clinical Evidence and Economic Considerations in Formulating Recommendations

Gurvaneet Randhawa, Agency for Healthcare Research and Quality (AHRQ)

Although it does not write guidelines, AHRQ supports the National Guideline Clearinghouse[14] and the U.S. Preventive Services Task Force (USPSTF), which issues recommendations on clinical preventive services.[15] The process that the USPSTF uses to generate recommendations is similar to those used by the NCCN and ASCO for guidelines.

[13] Hayes, Daniel F., Jeff Allen, Carolyn Compton, Gary Gustavsen, Debra G. B. Leonard, Robert McCormack, Lee Newcomer, et al. "Breaking a Vicious Cycle." *Science Translational Medicine* 5, no. 196 (July 31, 2013): 196cm6. doi:10.1126/scitranslmed.3005950.

[14] Information on the National Guideline Clearinghouse is available at http://www.guideline.gov/index.aspx.

[15] Information on the USPSTF is available at http://www.uspreventiveservicestaskforce.org/.

When creating a recommendation for a clinical test, considerations include the accuracy and performance of the test (analytical validity), the accuracy of the test in a defined population and clinical context (clinical validity), and the potential benefits and harms of the test. It is also important to evaluate the outcomes of the actions taken based on the results of the test. The results of such downstream actions are measured by surrogate outcomes, health outcomes, or (rarely) economic factors. There is generally good evidence for analytical and clinical validity, but not for outcomes.

Considerations for evaluating therapeutics are similar to those for evaluating tests. For example, the benefits and harms of a therapeutic are assessed in a defined population and clinical context. Evidence is typically better for short-term and surrogate outcomes than for long-term and direct outcomes; however, how well surrogate markers predict health outcomes is often unclear. Although the evidence base for evaluating therapeutics is better than for diagnostics, many knowledge gaps remain. Guidelines-setting panels and organizations, therefore, typically consider evidence uncertainty and contextual issues in addition to the magnitude of benefits and harms.

There are several challenges to formulating clinical recommendations. More and better evidence exists for efficacy (i.e., clinical benefits under ideal or controlled conditions) than for effectiveness (i.e., benefits under routine or real-world conditions). This could be addressed by comparative effectiveness research and patient-centered outcomes research. Similarly, there is more evidence for short-term than long-term outcomes, which could be improved with greater emphasis on post-marketing surveillance and by leveraging clinical informatics to connect diverse databases and analyze big data. Resource constraints often preclude economic analyses from evidence evaluation, and opportunity costs are rarely considered. Finally, evaluation of genetic technologies is further complicated by the need to consider mutations inherited by family members, the fact that the pace of technology development often quickly renders recommendations obsolete, and the incongruence between the traditional pharmaceutical blockbuster drug business model and drug development for rare diseases.

Looking forward, groups who issue clinical recommendations would benefit from improved efficiency of research and systematic reviews, more information on health care delivery systems, and greater transparency of economic evaluations.

Discussion

Moderator: David Veenstra, University of Washington

Discussion focused on the relevance of cost-effectiveness information for clinical guidelines. Both Robert Carlson and Hayes agreed that information on cost-effectiveness could affect guidelines, provided the information is reliable, reproducible, and efficiently produced. Tumor biomarker tests are often used to determine which patients *not* to treat, rather than which patients to treat. Alternatively, biomarker tests can be used to determine whether to perform other, more costly diagnostics. Thus, reliable cost-effectiveness information might help providers determine whether certain biomarker tests are worthwhile.

Williams noted that clinical utility data are necessary to produce cost-effectiveness measures. He suggested that economic tools could be used to determine the most important data gaps and focus research on where it matters most. Such analyses could be performed from multiple perspectives, including that of patients, payers, and providers. Hayes added that patient advocates are often effective in focusing cancer research efforts on the issues that matter most for patients.

PANEL 4: INSURERS, PAYERS, AND HEALTH TECHNOLOGY ASSESSMENT

Key Issues for the Centers for Medicare & Medicaid Services

Steve Phurrough, Centers for Medicare & Medicaid Services (CMS)

Statutes and regulations dictate payments made by CMS; clinical evidence is not typically a direct factor in payment decisions. Items and services must be classified within legally designated benefit categories in order to be eligible for CMS payments. For example, statutory guidelines prohibit CMS from paying for diagnostic tests unless they are used for a diagnostic purpose in a symptomatic patient. Thus, CMS will not pay for broad panel tests in asymptomatic patients no matter the clinical benefits or cost savings. On the other hand, CMS is legally required to pay for specific screening services named by law.

Within eligible benefit categories, CMS is required to pay only for items and services with appropriate billing codes that are deemed reasonable and necessary as defined by providing improved net health benefit over a currently available item or service. In practice, services are assumed reasonable and necessary unless specifically non-covered. CMS will occasionally issue a national coverage decision to formally settle payment eligibility of a specific item or service. Clinical trials demonstrating superiority over current services are required in these cases. CMS has issued about 300 such decisions—a small proportion of the total number of items and services that CMS pays for—in its history.

The CMS national office does not pay bills directly; regional contractors manage payments based on guidance from the national office. In the absence of guidance, however, each contractor makes independent payment decisions. Regional variation exists in payments for genomic tests because CMS has not issued national coverage determinations for them.

CMS maintains four major payment systems: inpatient hospital, outpatient hospital, physician fee-for-service, and clinical laboratory charges. The payment scheme for clinical laboratory tests will change in 2017. In the current system, CMS pays the originally established price for each clinical laboratory test. In the future, CMS will pay the average price paid by private insurance companies. CMS will require clinical laboratories to provide records of payments from private insurers in order to set the new prices. Additional add-on or pass-through payments from CMS require evidence of substantial clinical improvement demonstrated by superiority trials.

How Do Health Plans Approach Coverage for New Technology?

Jennifer Malin, Anthem, Inc.

Evidence of clinical utility is the primary criterion used by health insurance plans to determine coverage for new technologies. Cost is generally not a major consideration. Insurance companies have limited tools to implement coverage restrictions. These tools include claims audits and prior authorizations, which require providers to contact the insurance company to request coverage prior to providing a clinical service.

Malin identified four challenges pertaining to precision medicine. First, she noted that the field might be irrationally exuberant about the potential benefit of genetically targeted treatments. With a few notable exceptions including pertuzumab and imatinib, trials of targeted cancer therapies have yielded only marginal gains in survival. Malin advocated investigating clinical value earlier in the drug development process, pointing to a need for greater scrutiny of power and sample size calculations of clinical trials designed to detect modest effect sizes.

Second, clinical guidelines have begun adopting broad testing approaches in the absence of evidence. For example, although the NCCN guidelines for non-small cell lung cancer appropriately recommend epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) testing—both of which are linked by evidence to targeted therapies—they also recommend genomic panel testing that produces results that are not clearly actionable based on current evidence.

The third challenge is direct-to-consumer advertising. Many cancer treatment centers, which are often seen by patients as trustworthy, conduct their own in-house testing with unknown analytic validity. These cancer centers advertise their genetic tests directly to consumers, even though the analytic and clinical validity is unknown because the tests are proprietary, conducted in-house, and essentially unregulated.

Finally, Malin noted that litigation risk drives many business decisions. She therefore urged researchers to consider how to present scientific evidence so that it is actionable for an audience more concerned about litigation risk than the quality of scientific information.

Challenges to Advancing Personalized Medicine

Naomi Aronson, Blue Cross and Blue Shield Association (BCBSA)

Aronson reflected on the major themes of discussion and highlighted several challenges to further progress in personalized medicine. She noted that personalized medicine must be defined as broader than genomic medicine. For example, comorbidity of chronic diseases is a critical issue for the personalization of care that has been recognized but for which there are no clinical guidelines. Considering stratified medicine more broadly than genomics can help make heterogeneity in clinical trials and clinical practice more manageable. Efforts such as those by

the Center for Assessment Technology and Continuous Health are needed to identify common patterns of disease that predict treatment response and prognosis.[16]

Managing, interpreting, and making decisions based on the vast information produced by next generation sequencing tests likely presents a greater challenge than the costs of those tests. Researchers should consider how to better manage the cascade of new information. Incentives are also needed to align practice with emerging evidence.

Clinical evidence should be considered before cost, yet both cost and cost-effectiveness are also important. Cost is, in essence, a patient-centered outcome. For example, cancer patients fear their disease, fear the treatment, and fear the prospect of leaving their families with a financial crisis. Although some have claimed that personalized medicine will make treatments more cost-effective and valuable, greater personalization will also spread development costs over smaller populations. As common diseases are split into more specific and less common subtypes, the economic issue of affordability will become increasingly important.

Discussion

Moderator: Josh Peterson, Vanderbilt University Medical Center

Hayes discussed the FDA's evolving policies for regulating laboratory-developed tests. In the past, the FDA has allowed any laboratory certified by the Clinical Laboratory Improvement Amendments (CLIA) to develop its own tests, which may have resulted in the proliferation of tests that are not clinically or analytically valid. The FDA recently signaled that it might begin to scrutinize laboratory-developed tests more closely. Hayes advocated for greater oversight, arguing that it would level the playing field by treating diagnostics more like therapeutics and would spur innovation.

Hayes also suggested that cost analyses of expensive genomic tests such as Onco*type* DX® might reveal that they are cost-effective because they prevent unnecessary subsequent treatments. Malin noted that avoidance of chemotherapy is already included in the price structure of Onco*type* DX®. Moreover, chemotherapy is often administered even when Onco*type* DX® results suggest that it should not be.

[16] Information on the Center for Assessment Technology and Continuous Health is available at www.catch-health.org

PANEL 5: PHARMACEUTICAL AND DIAGNOSTICS DEVELOPERS, MANUFACTURERS, AND REGULATORS

GE Healthcare

Mitchell Higashi, GE Healthcare

GE Healthcare, primarily known as an imaging company, is interested in learning how biomarkers can inform the rational use of imaging. The company is building capabilities in medical diagnostics, life sciences, and health care information technology.

Genomic technology is growing in parallel to the connectivity of machines. Computing has grown exponentially over the past 110 years, driven in part by Moore's Law, which observes that the density of integrated circuits doubles approximately every 2 years. By 2016, an estimated 1 million petabytes (1 zetabyte) of data will be transmitted annually via the internet. Now, for example, magnetic resonance imaging (MRI) machines generate data, can communicate data quickly, and can even indicate when they are available for use.

GE Healthcare seeks to leverage advances in genomics and information technology by developing an agent-based simulation-modeling platform that incorporates likely patient behaviors to map how individuals will interact with providers and with each other. The goal is to develop a digital map that can be used to test different policy interventions and assess the incremental value of added genomic data. Simulated projections can then be used to drive informed decision making.

FDA and Personalized Medicine

Richard Moscicki, Food and Drug Administration

The goal of personalized medicine—as defined by identifying the right medicine, at the right dose, at the right time, for the right patient—is well aligned with the FDA's mission to improve benefits and reduce risks from the use of medications. Targeted therapies have grown from about 5 percent of new drug approvals in the 1990s to 45 percent in 2013. Most products with FDA breakthrough designation (80 percent) and orphan drug status (60 percent) are targeted treatments. In addition, approximately 65 approved drugs—not all of which are targeted—bear labels indicating the use of pharmacogenomics to inform their best use.

The targeting of treatments has brought both new opportunities and new risks to drug development. Targeted therapy programs have reduced drug development times by 2 years. Targeting defines diseases into smaller subsets, thereby transforming common diseases into rare diseases and rare diseases into ultra-rare diseases. Treating smaller populations of patients reduces development times and tends to produce larger effect sizes. Smaller trials may also, however, pose regulatory challenges by increasing uncertainty about risk.

Reliable companion diagnostics are critical for targeted treatments to produce optimal outcomes. Diagnostic tests should be vetted and continuously updated with new information.

The FDA actively works with the research community to develop new biomarkers and recognizes that many biomarkers fail because of lack of reproducibility.

The FDA's Critical Path Initiative anticipated the interdependency of drugs and diagnostic tests in 2004. Recognizing this new dynamic, the FDA created new staff positions and working groups to coordinate multiple efforts, developed new tools and pathways to engage with sponsors, issued many new guidance documents for drug developers, held public meetings, and established new collaborations and public-private partnerships. For example, the FDA's participation in the Biomarker Consortium helps shape the environment to facilitate biomarker development. These and other efforts enabled the FDA to approve 13 targeted therapies and their associated companion diagnostics within timeframes established by the Prescription Drug User Fee Act and the Medical Device User Fee and Modernization Act.

The most critical factor for the success of personalized medicines is the scientific understanding of molecular and genetic pathways of disease. Successes have been realized in oncology and with antivirals and, to a lesser extent, in certain psychiatric and genetic diseases because of advancements in our understanding of disease mechanisms. In contrast, personalized medicine has made less progress in diseases where the scientific understanding lags, such as Alzheimer's disease. The FDA has demonstrated that it can quickly approve new targeted treatments when good scientific evidence exists.

An Industry Perspective on Enablers of Patient Access in the Era of Personalized Medicine

Diego Ossa, Novartis

The concept of personalized medicine has gained momentum in recent years. Despite successes, progress in the development and use of personalized medicine has been slower than expected. This is because the science has proved more complex than expected and because economic incentives are misaligned. Regulatory and reimbursement policies need to be better integrated to spur innovation and support the development of clinical utility data for decision making. Although challenges remain, the science continues to develop fast and the promise for personalized medicine remains high.

The pricing and reimbursement framework is a key component for driving innovation and evidence generation; however, current reimbursement frameworks do not incentivize the industry to pursue personalized medicine approaches. Reimbursements for treatments and diagnostics remain separate, creating poor incentives especially for diagnostic development. Misaligned incentives negatively impact the health care system overall, and companies are reluctant to generate evidence for diagnostics beyond analytical validity without reason to expect a return on investment. Nonetheless, generating evidence of clinical utility and value from personalized medicine approaches is feasible. Evidence from nine case studies suggests

that drug developers and public research entities are engaged in such work.[17] The role for diagnostic manufacturers is less clear.

Also, decision makers have demonstrated willingness to consider evidence from well-designed studies that are not necessarily randomized controlled trials. An example of this is the National Institute for Health and Care Excellence (NICE) Diagnostics Assessment Programme in the United Kingdom. Established in 2009, this program evaluates innovative medical diagnostic tests based on clinical and cost effectiveness. By the end of 2014 the program produced 15 guidance documents and assessed 42 technologies, of which 62 percent were recommended for use, 19 percent were recommended for research purposes only, and 19 percent were rejected. There remains a need to assess the impact of NICE's recommendations on adoption of recommended diagnostics at the local level.

Looking forward, many challenges for the adoption of personalized medicine remain. Incentives for evidence generation and rewards for added value from innovative technologies that are not treatments are still unclear. Current reimbursement frameworks do not respond to the value-based approach needed to promote personalized medicine. As such, innovative reimbursement frameworks can be better suited to recognize and reward the value added by molecular diagnostics. For instance, integrated reimbursement for treatments and diagnostics would incentivize companies to pursue parallel development strategies and generate the required evidence for decision making (i.e., clinical utility). Similarly, performance-based pricing and risk sharing would incentivize quality and value metrics necessary for determining the added value of diagnostics in practice. Overall, the reimbursement system should be reformed to provide clarity on the return on investment and a clear path for funding and guidance on implementation.

The science, however, continues to move fast. Better economic incentive frameworks are needed to overcome current challenges and ensure future access to personalized medicine.

Discussion

Moderator: Peter Neumann, Tufts Medical Center

Participants briefly discussed the question of how personalized medicine should be defined. Although many agree that personalized medicine is not limited to genetics and biomarkers, conversations about personalized medicine tend to focus on those subjects. It may be more difficult to define what is *not* personalized medicine than to define what is personalized medicine. Basu suggested that a business case could be developed to define the scope of personalized medicine.

[17] Towse, Adrian, Diego Ossa, David Veenstra, Josh Carlson, and Louis Garrison. "Understanding the Economic Value of Molecular Diagnostic Tests: Case Studies and Lessons Learned." *Journal of Personalized Medicine* 3, no. 4 (October 25, 2013): 288–305. doi:10.3390/jpm3040288.

Much of the discussion focused on the optimal payment structure for genomic and other diagnostic tests. Mandelblatt expressed concern that CMS's reimbursements for diagnostics will be based on market rates, which have little relationship to the actual cost of testing. Phurrough reiterated that the CMS payment structure is mandated by legislation. He noted that CMS will soon publish a rule clarifying the forthcoming changes to the clinical laboratory payment system, and that a draft of the rule will be open for public comment prior to its finalization.

Several participants argued that a value-based approach to pricing is needed to incentivize and reward innovation. It was noted that, although not based on their clinical value, the price of therapeutics does include recovery of research and development costs. The long-term sustainability of innovative industries depends, in part, on their ability to provide investors an attractive return on investment. The growth of generic drugs, which now account for a large majority of prescriptions in the United States, has complicated the business model of pharmaceutical innovation. In the future, proliferation of targeted treatments that are effective for smaller patient populations may drive higher prices and pose a new challenge to the industry.

Summary Discussion

Moderator: Scott Ramsey, Fred Hutchinson Cancer Research Center

The workshop concluded with a summary discussion in which participants reflected on the themes raised throughout the meeting and suggested possible paths forward. Investigators expressed a desire to produce useful tools and information that could influence clinical guidelines and health care systems.

Representatives of integrated health systems offered suggestions for increasing the relevance of research on the economics of personalized medicine for their organizations. Vertically integrated health systems have a unique potential to align economic incentives and clinical care. Such health systems are interested in economic and decision analysis tools to compare costs and cost-effectiveness in order to make appropriate operational decisions. It is critical, however, that decision analysis tools and their output metrics are oriented toward systems-level questions.

Kaiser Permanente has a dedicated Interregional New Technologies Committee that examines clinical evidence and cost-effectiveness. The committee considers a range of outcome measures, including cost-per-quality-adjusted life year saved and health outcomes, although disconnects sometimes occur between the modelers and decision makers. Lieu suggested that different decision makers consider different outcomes and that the best way to increase the relevance of the cooperative agreement projects would be to present results in multiple formats. Williams added that transparent models are especially useful because decision makers can then alter the parameters and populate the models with local data to meet their needs.

Finally, participants suggested that it might be useful to draft a manuscript that connects the research and health care delivery enterprises and encourages increased communication

between these fields. Influencing clinical guidelines and reimbursement policies involves a long process. Proposals for optimized reimbursement frameworks and tools to influence payer behavior are also needed to encourage continued innovation in personalized medicine.

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Workshop Agenda

February 25, 2015
NIH Main Campus, Building 31, Room 6C10

Rev. 2-22-15

9:30 a.m.	Welcome and Introductions	Gregory Bloss Scott Ramsey
	Research Presentations	
9:45 a.m.	*Rational Integration of Genomic Healthcare Technology*	Josh Peterson
10:00 a.m.	*Value of Personalized Risk Information*	David Kent Peter Neumann
10:15 a.m.	*Personalized Medicine Economics Research*	Anirban Basu Josh Carlson David Veenstra
10:30 a.m.	*Optimizing Personalized Care Using Economic Studies of Cancer Genomic Testing*	Scott Ramsey Jeanne Mandelblatt Tracy Lieu
10:45 a.m.	**Break**	
	Panel Presentations and Moderated Discussions	
11:00 a.m.	Panel 1: *Health Care Providers* Moderator: Tracy Lieu	Allison Kurian, Stanford Bruce Blumberg, Kaiser Marc Williams, Geisinger
11:45 a.m.	Panel 2: *Patient Advocates* Moderator: Anirban Basu	Shelley Fuld Nasso, NCCS Bray Patrick-Lake, CTTI
12:30 p.m.	**Lunch**	Building 31 Cafeteria
1:30 p.m.	Panel 3: *Perspectives on Formal Guidelines* Moderator: David Veenstra	Robert Carlson, NCCN Gurvaneet Randhawa, AHRQ Daniel Hayes, ASCO
2:15 p.m.	Precision Medicine Initiative at NIH	Teri Manolio, NHGRI

2:30 p.m.	Panel 4: *Insurers, Payers, and Health Technology Assessment* Moderator: Josh Peterson	Steve Phurrough, CMS Jennifer Malin, Anthem Naomi Aronson, BCBSA
3:15 p.m.	**Break**	
3:30 p.m.	Panel 5: *Pharmaceutical and Diagnostics Developers, Manufacturers, and Regulators* Moderator: Peter Neumann	Richard Moscicki, FDA Diego Ossa, Novartis Mitchell Higashi, GE Health
4:15 p.m.	Summary Discussion Moderator: Scott Ramsey	All workshop participants
5:00 p.m.	**Adjourn**	