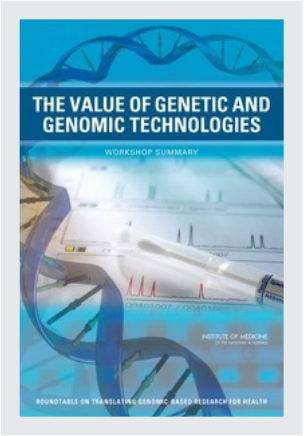

The Value of Genetic and Genomic Technologies: Workshop Summary

DETAILS

108 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-15771-1 | DOI 10.17226/12947

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THE VALUE OF GENETIC AND GENOMIC TECHNOLOGIES

W O R K S H O P S U M M A R Y

Theresa Wizemann and Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This project was supported by contracts between the National Academy of Sciences and the American College of Medical Genetics (unnumbered contract); American Medical Association (unnumbered contract); American Nurses Association (unnumbered contract); Blue Cross and Blue Shield Association (unnumbered contract); Centers for Disease Control and Prevention (Contract No. 200-2005-13434); College of American Pathologists (unnumbered contract); Department of Veterans Affairs (Contract No. V101(93) P-2238); Eli Lilly and Company (Contract No. LRL-0028-07); Genetic Alliance (unnumbered contract); Genomic Health, Inc. (unnumbered contract); Health Resources and Services Administration; Johnson & Johnson (unnumbered contract); Kaiser Permanente (unnumbered contract); National Cancer Institute (Contract No. N01-OD-4-2139, TO#189); National Heart, Lung, and Blood Institute (Contract No. N01-OD-4-2139, TO#189); National Human Genome Research Institute (Contract No. N01-OD-4-2139, TO#189); National Institute of Child Health and Human Development (Contract No. N01-OD-4-2139, TO#189); National Society of Genetic Counselors (unnumbered contract); Pfizer Inc. (Contract No. 140-N-1818071); and the Secretary's Advisory Committee on Genetics, Health, and Society (Contract No. N01-OD-4-2139, TO#189). Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number-13: 978-0-309-15771-1
International Standard Book Number-10: 0-309-15771-4

Additional copies of this report are available from The National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

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Suggested citation: IOM (Institute of Medicine). 2010. *The value of genetic and genomic technologies: Workshop summary.* Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not endorse the final draft of the

report before its release. The review of this report was overseen by **Elena O. Nightingale,** Scholar-In-Residence, Institute of Medicine, Washington, DC. Appointed by the Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

Acknowledgments

The support of the sponsors of the Institute of Medicine Roundtable on Translating Genomic-Based Research for Health was crucial to the planning and conduct of the workshop, The Value of Genetic and Genomic Technologies. Federal sponsors are the Centers for Disease Control and Prevention; Health Resources and Services Administration; National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute for Child Health and Human Development; National Human Genome Research Institute; the Secretary's Advisory Committee on Genetics, Health, and Society; and the Department of Veterans Affairs. Non-federal sponsorship was provided by the American College of Medical Genetics, the American Medical Association, the American Nurses Association, Blue Cross and Blue Shield Association, the College of American Pathologists, Eli Lilly and Company, Genetic Alliance, Genomic Health, Inc., Johnson & Johnson, Kaiser Permanente, the National Society of Genetic Counselors, and Pfizer Inc.

The Roundtable wishes to express its gratitude to the expert speakers whose presentations examined the value that genomic and genetic technologies play in existing clinical practice. These speakers were Bruce Blumberg, Marc Boguski, Wylie Burke, Roy Gandolfi, Anna Garrett, Karen Kaplan, Arthur Lurvey, Don Lyman, Elizabeth Mansfield, Dennis Salisbury, Andrew Spiegel, Vance Vanier, David Veenstra, Catherine Wicklund, Janet Williams, Marc S. Williams, David Witt, and Steven Woolf.

The Roundtable also wishes to thank the members of the planning committee for their work in developing an excellent workshop agenda. Planning committee members were Bruce Blumberg, Denise Bonds, Ralph Coates, Sharon Kardia, Muin Khoury, Michele Lloyd-Puryear, Catherine Wicklund, and Marc S. Williams. Thanks also go to Marc S. Williams for moderating the entire workshop.

Contents

BOXES

Abbreviations and Acronyms

ACMG	American College of Medical Genetics
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
COAG	Clarification of Optimal Anticoagulation Through Genetics
DRG	diagnosis-related group
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendments Act
FISH	Fluorescence In Situ Hybridization
GAPPNet	Genomics Applications in Practice and Prevention Network
GINA	Genetic Information Nondiscrimination Act of 2008
GWAS	genome-wide association study
HMS	Harvard Medical School
HNPCC	hereditary non-polyposis colorectal cancer
IHC	immunohistochemistry
INR	International Normalized Ratio
IWPC	International Warfarin Pharmacogenetics Consortium

1

Introduction

Slight variations in genetic composition can contribute greatly to the diversity which we see amongst individuals, from determining eye color and height to increasing the risk of developing breast cancer or heart disease. Numerous gene–disease associations are now known, and genetic/genomic testing is a relatively common laboratory approach for diagnosing presymptomatic genetic disorders, confirming an expressed genetic disease, screening for markers of increased risk of disease, or determining if someone is an asymptomatic heterozygous carrier of a recessive disease. Genetic or genomic testing can be used to guide medical decision-making and treatment, ranging from personalized drug therapy to assessing an individual's risk of developing common chronic diseases. However, these new technologies have not been widely integrated into clinical practice and the question remains as to how these advances are valued in the health care setting.

The Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health was established in 2007 to foster dialogue and partnerships that will advance the field of genomics and improve the translation of basic genomic research to applications in health care, education, and health policy. Wylie Burke of the University of Washington, and chair of this roundtable, said that the discussions have brought to light some of the very diverse perspectives regarding which genomic applications will be potentially useful in practice as well as what represents compelling evidence to bring an application into the healthcare setting. A need was identified for a workshop to explore the concept of value in regards to genomics and genetics and how that concept affects the views of stakeholders and the ways they make decisions about using these tests and technologies.

BOX 1-1
Definitions

Analytic validity The accuracy and reliability of the test in detecting the genetic changes of interest.

Clinical validity The accuracy and reliability of the test in identifying patients with the disorder of interest.

Clinical utility The possibility that the test will lead to improved health.

Diagnostic test A test to confirm a specific condition.

Prognostic test A test which predicts the possibility of developing a specific condition.

On March 22, 2010, the roundtable convened a public workshop to examine the perceived value of genetic and genomic technologies, both present and future, in clinical practice from the perspectives of different stakeholders.[1] The workshop was designed to build on the concepts of analytical validity, clinical validity, and clinical utility (Box 1-1) as well as the concepts of personal utility, public utility, and economic value, and to explore these concepts through questions such as:

- How do different stakeholders define the value of genetic and genomic technologies?
- How do stakeholders prioritize various aspects of genetic tests when determining value?
- How do people assess the relative value of genetic tests when making personal health care decisions?
- How do these types of value relate, or not relate, to the monetary cost of the technologies?

To facilitate discussion of the concepts, three specific case examples of genetic/genomic tests currently in use were presented, representing a range of different applications and spanning a range of opinions regarding their value: genetic testing for Lynch syndrome in colorectal cancer patients;

[1] The planning committee's role was limited to planning the workshop. This workshop summary has been prepared by a rapporteur as a factual summary of what occurred at the workshop. Statements and opinions are those of individual presenters and participants and should not be construed as reflecting any group consensus.

pharmacogenomic testing for warfarin dosing; and genomic profiling. Following the reactions of the expert panel to each scenario, there was open discussion with stakeholders, including patients, clinicians, payers, policy makers, and other workshop participants. The discussion was intended to focus not on the value of the specific treatment or test presented, but rather on the broader issues of how each individual stakeholder derives his or her personal or professional opinion of the value of using the technology.

Chapters 2 through 4 of this report summarize the discussions of each clinical scenario by the expert panelists and provide highlights of the open discussions. Closing remarks are provided in chapter 5. The three case studies are presented in full in the appendixes, along with the workshop agenda and biographical sketches of the panelists.

2

Tumor-Based Screening for Lynch Syndrome

In presenting the first clinical scenario, Marc Williams of Intermountain Healthcare's Clinical Genetics Institute described how tumor screening and confirmatory genetic testing for mismatch repair gene mutations are being used to identify Lynch syndrome in individuals who are newly diagnosed with colorectal cancer.[1] The intent is that family members of those with Lynch syndrome would then be screened, so that those identified as also having Lynch syndrome could take preventative measures in hopes of reducing their morbidity and mortality from colorectal cancer.

COLORECTAL CANCER AND LYNCH SYNDROME SCREENING

Colorectal cancer is the second leading cause of cancer death in the United States, accounting for about 50,000 deaths per year and affecting almost 150,000 people each year. One in every 19 people will be diagnosed with colorectal cancer in their lifetimes, and one person dies from the disease every nine minutes. About 5 to 10 percent of colorectal cancer cases are familial, and it is estimated that about 1 to 5 percent of cases are due to mutations in highly penetrant single genes. A subset of these mutations cause Lynch syndrome, sometimes referred to as hereditary non-polyposis colorectal cancer (HNPCC) because individuals with the syndrome tend to have a relatively small numbers of polyps. Lynch syndrome may account for as much as 2 to 4 percent of all colorectal cancers, and it also increases an

[1] The complete scenario provided to workshop participants is available in Appendix C.

individual's risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, skin, and prostate as well as, among women, endometrial and ovarian cancer.

Diagnosing Lynch Syndrome

Lynch syndrome is associated with mutations in four major mismatch repair (MMR) genes (*MLH1, MSH2, MSH6,* and *PMS2*), and individuals who have one of these mutations have a 20 to 65 percent lifetime risk of colorectal cancer, compared with a lifetime risk among the general population of approximately 5 percent. Because inheritance of these mutations is autosomal dominant, close biological relatives are also at high risk.

Classic signs that suggest an individual may have Lynch syndrome include: a family history of colorectal and associated cancers, specific pathologic characteristics of the tumors, a young age of onset, and synchronous or metachronous colorectal cancer. However, these signs, either alone or in combination, are not sufficiently sensitive to identify more than about 50 percent of patients with Lynch syndrome. A new strategy has been proposed to screen the tumors of patients presenting with colorectal cancer, using techniques designed specifically to identify Lynch syndrome (e.g., immunohistochemical (IHC) staining for the protein products of the four MMR genes or an assessment of the tumor for microsatellite instability (MSI)). If the tumor screening is positive, a mutation analysis is done to confirm a diagnosis of Lynch syndrome.

Who Is Lynch Syndrome Screening for?

Screening for Lynch syndrome in a patient with colorectal cancer combines initial testing of tumors with mutational analysis to definitively diagnose the presence of MMR gene mutations.[2] A diagnosis of Lynch syndrome may have some effect on the patient's treatment as well as on monitoring for colorectal cancer recurrence and for other cancers associated with Lynch syndrome (e.g., increasing the frequency of colonoscopies or considering a prophylactic surgery, such as a hysterectomy and salpingo-oophorectomy, which are used to reduce the risks of endometrial cancer and ovarian cancer in women). However, the real impetus for testing is the potential effect of the diagnosis on close relatives. First-degree relatives have a 50 percent chance of having inherited the MMR gene mutation, and, on

[2] Due to the cost of MMR gene sequencing, preliminary tests, including microsatellite instability (MSI) testing and immunohistochemistry (IHC), are often conducted first to identify those who should be offered DNA sequencing. Further details regarding the screening process for Lynch syndrome are provided in the case scenario in Appendix C.

average, there are three affected family members for each proband (i.e., for each of the first subjects in a study).

In the United States, there are 142,000 newly diagnosed cases of colorectal cancer annually and, assuming a 3 percent prevalence rate, about 4,250 of those individuals have Lynch syndrome. This means that around 8,500 to 12,750 relatives would also be carrying one of these mutations and also have Lynch syndrome.

Based on evidence reviews, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has reported that the overall analytic validity of the preliminary and diagnostic genetics tests for Lynch syndrome is high, there is adequate evidence of clinical validity for the preliminary and diagnostic tests, and there is adequate evidence to support the use of genetic testing strategies to reduce morbidity and mortality in relatives with Lynch syndrome (i.e., high rates of relatives consent to testing and adhere to recommended cancer surveillance recommendations, and there are limited harms compared to benefits) (EGAPP Working Group, 2009).

Testing of family members is much less expensive than primary diagnostic testing, since only the specific familial mutation is tested for (i.e., full gene sequencing is not necessary). For those related individuals who are identified as having Lynch syndrome, endometrial screening in female carriers or prophylactic surgery, or both, may also be appropriate, as well as more frequent colonoscopies, starting at an earlier age. There are also effective interventions if precancerous polyps are detected. Because of these facts, EGAPP has recommended offering screening followed by confirmatory genetic testing for Lynch syndrome in individuals newly diagnosed with colorectal cancer to reduce morbidity and mortality in relatives (EGAPP Working Group, 2009).

Costs and Benefits of Implementation

Using published data, Mvundura and colleagues conducted a cost-effectiveness analysis and found that, from a U.S. healthcare system perspective, tumor-based screening for Lynch syndrome is cost effective and that an IHC-first approach is superior (Mvundura et al., 2010). Offering the perspective of an integrated healthcare delivery system, Williams explained that Intermountain Healthcare has modeled various screening scenarios and has also concluded that a strategy using IHC as the preliminary test appeared to be the most efficient. Following a decision pathway based on screening results makes it possible to sequence only one or two specific genes, as opposed to sequencing all four. Overall, this strategy has improved the quality and consistency of care at Intermountain Healthcare. Because the screening is done on the tumor, the hospital pays for the cost of screen-

ing out of the diagnosis-related group (DRG) reimbursement it receives, which reduces profit margins. However, there is the potential to increase revenue for providers, hospitals, and outpatient surgery centers, Williams said, because of the increased periodicity of screening and also because of the potential for family members to enter the system as new patients. There will be small increases in costs for health plans because they would need to cover confirmatory mutation testing as well, but there is also the potential for savings by avoiding significant costs as a result of prevention of cancer, particularly in relatives that may also be covered.

From a patient perspective, screening provides information on surveillance, it may affect treatment, and it may offer a better prognosis. Privacy issues remain a concern, Williams said, but they may be somewhat mitigated as patients already have expressed colorectal cancer. For family members, identification of high-risk individuals provides opportunities for primary prevention and, in roughly one-half of at risk relatives, reassurance for family members who do not carry the Lynch syndrome mutation.

In implementing the Lynch syndrome screening system, Intermountain Healthcare provides patients with an information sheet, and it offers full counseling and consent for confirmatory mutation testing of both the patient and family members. However, it was decided after significant ethical consultation that informed consent was not needed for the tumor-based screening because it was not considered genetic testing but rather screening for susceptibility.

PANEL REACTION

Patient Advocate Perspective

From the perspective of the Colon Cancer Alliance, the oldest and largest national patient advocacy organization in the United States dedicated to colorectal cancer, there is great value in Lynch syndrome screening. The prospect that screening could help prevent some of the 50,000 colorectal cancer deaths that occur each year and, more importantly, prevent some people from ever experiencing this cancer, is very exciting, said Andrew Spiegel of the Alliance.

Spiegel highlighted several issues for further consideration. While Williams noted in his introduction that privacy is generally less of an issue for Lynch syndrome testing because close associates are already aware that the individual has colorectal cancer, Spiegel countered that patients with Lynch syndrome are also at a higher risk for ovarian, endometrial, and other cancers. An insurance company or potential employer who learns that a person carries the mutations that can cause Lynch syndrome now knows that the person is susceptible not only to colon cancer but also to other

cancers as well. Privacy is a major issue not only for the primary individual with colon cancer, Spiegel stressed, but also for the family members who are also identified as having Lynch syndrome. What assurances are there, he asked, that the test results will remain private?

Spiegel also raised concerns about informed consent, noting that tumor screening, while perhaps not a "genetic test," does suggest the presence of a specific genetic mutation, and the result is the same from the patient perspective—the patient either does or does not have Lynch syndrome. A number of questions surrounding such screening must be addressed, Spiegel said: Should informed consent be required for tumor screening to determine whether or not a patient is at risk for having Lynch syndrome? If the person does have Lynch syndrome, what kind of counseling will be provided, and should that counseling be mandatory? What is the responsibility to inform relatives of the proband, and what if the relatives do not want to know whether or not they carry Lynch syndrome mutations? Who bears the responsibility to notify family members that a parent or sibling has Lynch syndrome? If it becomes the responsibility of the patient, what happens if the patient fails to tell family members for certain personal reasons? Should a doctor refuse to treat a patient who refused to notify family members? Should it instead be the responsibility of the doctor to tell family members that they may carry the Lynch syndrome gene and that they should be tested? Or perhaps the State Department of Health? Under what authority can notification be forced? Spiegel also noted that criteria are needed for how to inform and for which family members will be told. Would such criteria be uniform across the country? Policies and procedures in a major city hospital may be very different from that in a rural setting. What follow-up will there be with family members who may be at risk for Lynch syndrome? Whose responsibility will it be to ensure those family members are screened and to make screening readily available and affordable?

Diagnostic Pathology Perspective

Mark Boguski of the Center for Biomedical Informatics at Harvard Medical School (HMS) and the pathology department at Beth Israel Deaconess Medical Center, a teaching hospital of HMS, offered the perspective of diagnostic pathologists. The problem with any single genetic test, Boguski said, is there are 24,000 human genes and single tests are not scalable. Laboratories already perform many hundreds of tests on tens of thousands of specimens daily. What will be the operational role of pathology, he asked, and what are the economic and efficiency implications of doing single gene tests in the age of whole genome sequencing and personalized medicine? Boguski suggested that in the not too distant future a patient's whole genome will be part of his or her existing electronic medical record.

Karyotyping or MSI testing, for example, will no longer be done and will instead have been replaced by whole genome or whole transcriptome (transcribed RNA) sequencing, or both, and carrying out different genetic screens will be a matter of applying different software filters. To prepare for this data-rich future, Boguski has begun a training program for HMS clinical pathology house staff to bring them up to date on genomics and personalized medicine, specifically the state of the field and the technology being used. Boguski concluded by noting that while the discussion at hand is about Lynch syndrome, the larger issue to be addressed is the ability to carry out individual genetic tests for 24,000 genes, the movement toward genome sequencing, and the software and decision support systems that will be the primary diagnostic modality in the near future.

Insurance Provider Perspective

Roy Gandolfi, a practicing internist and associate medical director of Select Health, offered perspective on the role of insurers and coverage decisions. As the insurance arm of Intermountain Healthcare, Select Health is a bit different from most other insurance plans. It is not for profit, it does not offer coverage for Medicare, and the median age of the 500,000 commercial lives it covers is 27 years old. The system is integrated: Select Health is owned by the parent company, Intermountain Healthcare, which also owns many hospitals and employs a significant number of the physicians who work for the system. So, while Select Health is an independent business entity, it is integrated within the larger health care system.

Intermountain has very strong fetal-maternal medicine programs at the university as well as at Intermountain hospitals. While these are invaluable resources, they also mean that Select Health is faced with more genetic decisions than other health plans with the same population. As a health plan, Select Health looks not only at guidelines but at how those guidelines were derived and their level of evidence. Medical technology is carefully reviewed, with a focus on looking at what the specific genetic test is trying to achieve, conducting evidence-based literature reviews, and seeking local input from providers regarding coverage recommendations. Alternative technologies are considered, and economics are assessed relative to all stakeholders: the hospitals, the plan as a payer, the plan members, and their employers, who pay for the insurance.

There are many genetic tests that have been proposed both commercially and academically, and, unfortunately, Select Health does not have the resources at the present time to evaluate all tests. How then, can the plan make coverage decisions if it is not able to conduct a medical technology review? Clinics are a valuable resource for gaining perspectives on clinical

utility and economics, Gandolfi said, as are experts at the Clinical Genetics Institute as well as local providers.

Select Health feels a responsibility to the employers who are paying the insurer to manage the care being provided, both for good health outcomes and for fiscal responsibility. For Lynch syndrome, for example, while the focus is on identifying affected relatives, it is also very important from the health plan perspective to look at the proband, because the treatment course for that patient will change if he or she has the genetic disorder. As such, Select Health feels it is important that coverage be applied to the Lynch syndrome test.

Private Practice Perspective

Dennis Salisbury, a family physician at Rocky Mountain Clinic in southwest Montana, said that he sees one or two colon cancer patients a year in his practice, out of several thousand patients total. This makes the process of deciding who gets what information—and making sure they have enough information without overwhelming them—rather challenging. He has come to rely on information gained elsewhere. Of key importance in the decision-making process for recommending a test is the clarity of the association between a condition and an outcome along with the validity and predictive value of the testing. Incidence and prevalence of the condition are both important, as is the severity of the impact of the condition and the significance of the potential benefit of the test. Costs must also be considered, relative to whether that patient is insured. Costs that could be avoided if testing is done are also a factor. Patient benefit, family benefit, and, to some degree, public benefit are all part of his decision-making process, Salisbury said. The biggest issue is educating the patient to facilitate his or her autonomous decision.

Since many in private practice do not have either the time or the expertise to assess the validity and predictive value of the testing, they rely on other sources, such as EGAPP recommendations. In this case, Salisbury said, he is firmly in favor of screening for Lynch syndrome in a patient with newly diagnosed colon cancer. The question then becomes how to present information about the test to patients so that they can make an informed decision. It is important to have good information about what the test can mean for a patient's future (e.g., how it can improve life, extend life, make life more complicated or more difficult, whether there will be complications associated with the testing, and if testing can help family members). Salisbury also noted that how a provider presents the information can sway a patient's decision.

Salisbury said he would be happy to be the one to tell family members of the test results, but he questioned what should be done if the proband

does not want a family member informed. If the family member is also a patient in the practice, this becomes a very difficult scenario, legally and ethically.

Public Health Perspective

Providing a government perspective, Don Lyman, chief of the Chronic Disease and Injury Control Division of the California Department of Public Health, said that as far as most official government agencies are concerned, there has not been any conclusion as to whether screening for Lynch syndrome is worthwhile or not.

Historically, profound issues tend to be addressed most productively at the local level first. The federal government may see the problem, but it often waits for several "strategic loci" (localities or states) to begin to address the issue locally. Once several jurisdictions have been through the process, the federal government looks for models that can then be applied nationally. The great advances in sanitation in the 1800s, for example, were first employed in the cities of Boston, Charleston, and Philadelphia. Environmental air quality got its start in California. Once several jurisdictions found a way to bring these problems under control, the federal government recognized the commonalities in the various successful approaches, passed national legislation, set policy, and provided national funding. In this regard, the activities occurring now at state, local, and private levels regarding genetic testing are very attractive, Lyman said.

The key questions concerning genetic testing are whether the ends justify the means and whether the means justify the ends. In a "utilitarian" approach, the end point is set, and then one does what can be justified to get to that endpoint. The whole genome project is a utilitarian approach, he said, and the question is how useful is it? The new paradigm for physicians in the 21st century is not to extend the length of life but rather to improve the quality of life. The genetic methodology under discussion is directly applicable to that goal, Lyman said. But from the point of view of a public official, it looks more like a solution in search of a problem; there is a process, it is very attractive, and a lot of money has been spent developing it. Now how can it be applied? What a public official wants to see is an application that brings measurable results for quality of life on a population basis and not for just a few people here and there. Drawing lessons from other public health initiatives that have measurably reduced illness and death rates, such as AIDS, drunk driving prevention, and the tobacco control program in California, could help identify useful approaches to the application of genomic science, Lyman said.

Cost savings is a tricky issue, Lyman said, and it is one that he does not take into account. There are cases of measurably productive, spectacular

interventions that have brought no cost savings at all. There is a disconnect between what the medical professional community does and what the insurance industry does. In the early 1950s for example, penicillin, the polio vaccine, and sterile surgical techniques were introduced; there were measurable changes in morbidity and mortality patterns; and still the cost of the industry went up.

It is the government's responsibility to take what looks credible and move with it. As a public health official, Lyman said, there is a point in the academic exercise when one has sufficient evidence to be able to reach a decision. But no one knows exactly where that point is. It takes meetings such as IOM workshops, published literature, and expert groups to help determine when enough is enough and when a disease control application can be moved along in order to induce measurable improvements in quality of life.

OPEN DISCUSSION

Privacy, Informed Consent, and Information Sharing

Privacy-related issues received a great deal of attention during the open discussion. Williams pointed out that while the Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits discrimination based on genetic information, it does not prevent discrimination based on manifest disease; that is, predispositional testing and the information obtained thereof are protected, but people who already express a disease are not protected under GINA for the purposes of insurance and employment. Spiegel added that a patient's insurance company knows if that patient has colon cancer because the insurance company is paying the medical bills, and the patient's employer may also know because, for instance, the patient needed time off from work for surgery. But the employer may not know that the patient has Lynch syndrome, which puts the patient at a higher risk of developing other cancers such as endometrial or ovarian cancer.

Boguski pointed out that companies like Microsoft and Google Health are not governed by HIPAA. When someone types "Lynch syndrome" into the Google search engine, both Google and the Internet service provider know where that search came from. Boguski mentioned an anecdote about Google being able to predict H1N1 flu trends ahead of the CDC, just by tracking people's search patterns. It is naïve, he said, to think that in such a world privacy can still be regulated in the traditional way.

Lyman mentioned California's cancer registry, one of the largest in the world. That database is primarily for research purposes, and patients are identified for studies or interventions based on the information in the cancer registry. There are strict protocols which have addressed most of the

privacy issues, but some still have concerns. The Veterans Administration, for example, has reluctantly agreed to report its cancer cases to the state cancer registries in California and elsewhere, but it will not allow names to be entered, which results in a large proportion of reported cancer cases that have been effectively removed from potential study.

Application of Genomic Testing

Data Gathering for Decision Making

A participant asked Williams for more information about the sources of the data and the resources used for Intermountain's modeling of various Lynch syndrome testing scenarios. Williams responded that the data were primarily from published studies but that Intermountain also contacted authors and asked if there were any additional data (i.e., "gray literature"). One university group had accrued a large set of IHC, MSI, and mutation testing data that they were in the process of preparing for publication and that they were willing to share with Intermountain Healthcare under an agreement. However, even this type of arrangement raises the larger issue of where to find resources to support the generation and analysis of this evidence. In this case, the IHC, MSI, and gene testing were done by a university under grant funding, and Intermountain Healthcare used available resources to support staff time to analyze the data and populate the models. However, many times those discretionary funds are not available.

An important question, Boguski said, is who is going to pay for the development and analysis of testing in the future. Would a genetic test be a commercially viable diagnostic developed by a biotechnology or diagnostics company? Would there be enough evidence for such a test—and enough of a market for it—that it would be developed and reimbursable? Beyond the basic research funding environment, how will these tests be developed?

There is a provision in the Food and Drug Administration Amendment Acts (FDAAA) of 2007 that is designed to trigger the collection of data from Medicare, Medicaid, and a number of private payers and ultimately to lead to the accrual of data about drug use in 145 million people in the United States, Williams said. If that effort is successful, it will provide numerous opportunities for analysis. Perhaps a similar approach could be applied to data collection for the results of genomic testing and screening programs, Williams said.

Another approach to data collection is the "coverage with evidence development" method that the Centers for Medicare and Medicaid Services (CMS) has put forward. As an insurer, Gandolfi said he must consider whether to pay for research and for the statistical analysis of that research from an unbiased source. The Blue Cross and Blue Shield Association established a

Technology Evaluation Center (TEC), and the independent Blue Cross and Blue Shield plans pay TEC to review and assess medical technologies for them. Select Health pays for a subscription to Hayes, an independent external technology assessment firm, because it does not have the necessary internal resources. Insurers need good-quality evidence in order to make coverage decisions. However, many of the studies that are available are underpowered, having not enrolled enough participants to support sound statistical analysis. Instead of funding such inefficient studies, Gandolfi said, resources should be directed toward studies that will produce useful evidence.

Burke observed that Lynch syndrome testing is an example of an emerging paradigm that falls somewhere between the individual patient care model of medicine and a public health model. The major benefit of tumor testing in one individual appears when other family members are tested and measures are taken to prevent cancers in those who are positively identified as having Lynch syndrome. There are no data yet regarding whether family members will, in fact, appear for testing when notified or what the outcomes of the screening will be. While screening is intuitively a good idea, evidence is needed, including how to effectively reach family members. If the evidence were to support the better health outcomes envisioned here, would this new model of healthcare be a good idea, Burke asked?

It would be a useful model for Lynch syndrome, Boguski said, however it is difficult to generalize it to other diseases. To achieve economies of scale, different approaches will be needed, he said. Beyond Lynch syndrome, it is not clear what other genetic conditions this approach might be applicable to and what kinds of technologies, processes, and payment systems will be needed to address those conditions. An alternative approach is needed.

The fragmentation of the healthcare system adds to the difficulty of making the economic cost case, Salisbury said, since family members are often covered under different health plans. Even so, the case could be made—and there are articles that support—the use of sequencing to test for the presence of such conditions as Lynch syndrome.

Lyman reminded the participants that the notion of diagnosing one person and then tracking down family members for treatment or prevention is not new. It has been done for many years, often with limited success. Fifty years ago, for example, it was known that there were risks associated with high blood pressure and that high blood pressure runs in families. Efforts to do blood pressure testing in family members failed, he said, but at least every doctor's office now has a blood pressure cuff. Nutritional counseling for patients with diabetes and their families is another example. In part, the doctor–patient, one-on-one medical model is standing in the way of reaching out beyond the individual patient.

A participant asked whether there was any reason, other than practicality, to focus Lynch syndrome screening exclusively on those with newly

diagnosed colon cancer? Is there any reason, for example, not to look back at cases of colon cancer that were diagnosed in the recent past? Williams responded that Intermountain has considered doing that and would have the capability of pulling those cases. Within its system, using individual patient data and publicly available genealogical data, the company also has the ability to construct linkages and identify families that would be considered at higher risk. Before expanding testing, the ultimate question that must be asked is, If people are presented with this information, will they act on it? Williams raised the issue of opportunity cost: If resources are invested in this approach and then it turns out it does not work, could that money have been better spent on some other program that would have resulted in better outcomes? What Intermountain Health is trying to do, he said, is to put out a number of different testable hypotheses. If it can be determined relatively rapidly that something is not going to work, then resources can be dedicated to something else.

In this regard, Williams said, Intermountain Healthcare made a decision, in conjunction with its pathologists, to not conduct Lynch syndrome screening tests in house. While it was agreed that conducting the testing in house would bring money into the system, it was also determined that Intermountain did not have as high a level of expertise as others, and sending the tests out would provide better quality of care. The reality is that performance will vary from laboratory to laboratory, and that can influence where resources should be invested.

Salisbury said that the clarity of the gene–disease association and the validity and predictive value of the test are significant issues that affect his decisions and how he counsels patients. Gandolfi noted that internists simply do not have the resources or the time to keep up on certain niches of medicine and need to rely on other resources that help them make decisions, including genetic counselors, geneticists, and oncologists.

Clinical Utility

A participant from the Office of the Air Force Surgeon General cited an article in which the authors assessed a cohort of about 1,500 colorectal cancer cases and identified 153 that were positive for Lynch syndrome. From all the examined cases, only one family member was ever referred based on genetic family history (Hampel et al., 2008). The participant noted that the same thing occurs at the Department of Defense: Families at risk are not identified based on family history. The question is, Does the screening test have utility beyond family history, and can it help fill the gap? Williams concurred, noting that in the vast majority of cases, family history is not applied well, and actually, in practice, sensitivity is going to be much lower than would be predicted.

Boguski suggested a hypothetical situation in which a large entity (e.g. Kaiser, the Department of Public Health, the Air Force) would sequence everyone it had access to and use that information to estimate the potential genetic disease burden in that population for disease that might not express itself for 20 or 30 years. He wondered if that approach would not be more cost-effective over the long term, compared to individual, specialized screening tests based on criteria that vary from one disease to another. A participant responded that what Boguski was suggesting was basically high-throughput next-generation sequencing. The error rate and reproducibility of such an approach is not yet known, the participant said. What is known is that there are neurological and other diseases that are not adequately diagnosed by these sequencing technologies and which may represent an important, complex disease burden. The participant cautioned that before potentially costly genome sequencing is broadly considered, it will be critical to make sure that the type of information obtained is validated. "Sequencing is highly overrated," he said. Boguski pointed out that once the sequencing approach has been validated and is reproducible, the economics will be clear. If, for example, a karyotype and fluorescence in situ hybridization (FISH) analysis costs $800 and a whole genome sequence costs $1,000, it would make economic sense to pursue an automated system that can provide readouts on the genetic burden for numerous diseases, rather than conducting one specific diagnostic test. Williams agreed that the advances in sequencing will transform the future, but those in practice cannot just wait for change. They need to have something they can do today.

3

Pharmacogenomic Testing to Guide Warfarin Dosing

In the second clinical scenario, David Veenstra of the Department of Pharmacology and the Institute of Public Health Genetics at the University of Washington described how pharmacogenomic testing could be used to guide initial warfarin dosing and management.[1] Because warfarin has a very narrow therapeutic range and because there is high inter- and intra-patient variability in response, finding the optimal dose can be challenging. While there are non-genetic factors that affect individual response, it is known that variations in two specific genes are associated with response to warfarin, and it has been suggested that pharmacogenomic-based dosing could speed up the determination of the appropriate initial therapeutic dose.

WARFARIN PHARMACOGENOMICS

Warfarin (known also by the brand name Coumadin) is an anticoagulant used for the prevention of thromboembolic events. Most commonly prescribed for patients with atrial fibrillation, it is also used to prevent clotting events in patients with mechanical heart valves or deep vein thrombosis as well as given prophylactically prior to major orthopedic surgery. Warfarin has been in use since 1954, and in 2004 more than 16 million prescriptions were dispensed in the United States. There are currently no direct competitor drugs on the market. Warfarin is highly effective, reducing the risk of ischemic stroke by more than 50 percent compared to aspirin

[1] The complete scenario provided to workshop participants is available in Appendix D.

and by nearly 70 percent when compared to cases where there is no antithrombotic therapy at all.

Initiation of Treatment

The International Normalized Ratio (INR), which is used to measure treatment response in patients receiving warfarin, is the ratio of the patient's prothrombin time to a control or "normal" sample, corrected for the sensitivity of the control reagent used relative to an international standard. If the INR is either too low or too high, the patient has a three times higher risk of a clotting or bleeding event, respectively. Serious, life-threatening bleeding events (those requiring medical intervention, such as gastrointestinal or intracranial bleeding) happen in about 2 to 10 percent of patients during the first year of warfarin treatment, and approximately 1 percent of these events are fatal. Warfarin is generally underutilized, particularly in the elderly, because of concerns about bleeding events.

It is well known that certain clinical and demographic factors influence warfarin dose requirements, including age, race, sex, co-morbidities, concomitant medications, and diet. A clinician will make adjustments in the starting warfarin dose based on such known factors. Once the patient begins taking warfarin, the clinician monitors the patient closely; the monitoring is initially performed once every three to four days, then it is done weekly or every two weeks, and then, once a patient is stable, maybe every four to eight weeks. As such, warfarin dose management can already be considered "personalized medicine." Still, a given patient's INRs are generally in the appropriate range only 50 to 70 percent of the time. The question then, Veenstra said, is whether genomics can be used to improve warfarin management.

Warfarin Genetics

There are two genes known to be involved in outcomes related to warfarin therapy. The first, *CYP2C9*, codes for an enzyme that is primarily responsible for the metabolism of warfarin. Early studies identified two variants, *2 and *3, that affect the half-life of the drug. Warfarin metabolism is reduced by 40 percent in patients with the *2 variant and by 90 percent in those with the *3 variant. The prevalence of these variants in populations varies by race, occurring most often in patients of European descent and least commonly in patients of Asian descent.

Variant *CYP2C9* genotypes account for about 10 percent of warfarin dosing issues. Clinical outcomes studies indicate that patients with the *2 or *3 variants have approximately twice the risk of a life-threatening bleeding event and that, during the first 90 days of therapy, that risk is

actually about four times higher (Higashi et al., 2002; Limdi et al., 2008). *CYP2C9* variants also affect the length of time required to achieve stable dosing. The hypothesis, according to Veenstra, is that with an increased half-life of warfarin, people with one of these gene variants are much slower to respond to dose adjustments. Correspondingly, Veenstra has observed that it takes, on average, three months longer to stabilize these patients compared to patients without the variant at the University of Washington anti-coagulation clinic.

The other gene of interest is vitamin K epoxide reductase, *VKORC1,* which codes for the warfarin drug target. The *VKORC1* genotype is responsible for 20 to 25 percent of the variation in the required warfarin dose. The "A" haplotype group of polymorphisms is associated with a lower required warfarin dose, while patients with group "B" haplotypes require higher doses (Rieder et al., 2005). Interestingly, unlike the case with the *CYP2C9* variants, *VKORC1* gene variants have not been found to be associated with bleeding risk.

The rationale for learning an individual's *CYP2C9* and *VKORC1* genotypes is that this information could guide the determination of the initial warfarin dose, allowing the clinician to stabilize the patient's INR more quickly, reducing the number of necessary office visits, and ultimately putting the patient at a lower risk of a bleeding event. While most of the studies to date have focused on the safety-related issue of reducing bleeding events, there are also issues of efficacy in terms of administering higher doses to patients who need them.

Pharmacogenetic Testing

There is convincing evidence of warfarin's clinical validity, Veenstra said. Testing for the select, informative *CYP2C9* and *VKORC1* single nucleotide polymorphisms is straightforward and the International Warfarin Pharmacogenetics Consortium has recently developed a warfarin dose prediction algorithm (IWPC, 2009) using findings from nine different countries and based on the relationship between dose requirements and the known clinical and genetic factors. The consortium found that estimating a starting dose using the pharmacogenetic algorithm resulted in a more accurate starting dose which was closer to the required stable therapeutic dose than starting doses estimated using clinical factors alone. The largest difference between estimation approaches was observed in patients who had high dose requirements—greater than 49 mg per week—although this was not a high proportion of patients. There was also some benefit of including genetic information when making estimates for patients who required low doses, less than 21 mg per week. Further support for the analytic and clinical validity of pharmacogenomic testing for warfarin has been provided by

a systematic review completed in 2006 by the American College of Medical Genetics (ACMG) (Flockhart et al., 2008).

While such studies support the clinical validity of pharmacogenomic testing to guide warfarin dosing, few studies have been done that provide direct evidence of clinical utility. Indeed, the 2006 ACMG report concluded that no study had shown testing to be effective in reducing high INRs, shortening the time to a stable INR, or limiting the number of serious bleeding events. A more recent systematic review by researchers at the University of California, San Francisco did not find sufficient evidence to support the use of genetic testing to guide warfarin therapy (Kangelaris et al., 2009). Additionally, the Clinical Practice Guidelines for the American College of Chest Physicians states explicitly that "we suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial" (Ansell et al., 2008).

Veenstra raised several issues that should be considered when the necessary randomized controlled trials are conducted, including: selection of comparator (should it be against an algorithm that uses clinical information, standard of care, or intense monitoring?); statistical power (if bleeding events are the primary outcome, the trial will require 5,000 to 10,000 patients to be sufficiently powered, assuming a 4 to 8 percent risk of a major bleed in the first year of therapy and a 25 percent relative risk overall); and use of surrogate markers (trials may be designed with the percentage of time that INR is in range as the primary outcome).

Veenstra described several randomized controlled trials that assessed or are in the process of assessing the impact of genotype-guided dosing on clinical outcomes. A study by Anderson et al. randomly assigned 200 patients to two groups that used either genetic information in addition to clinical information or else clinical information alone (Anderson et al., 2007). Overall, the investigators found no significant difference between these two groups in the time that INR was in range, but there did seem to be a trend toward benefit for certain patient groups. Another study by Caraco et al. reported a shorter time to first therapeutic INR and to first stable INR in patients using *CYP2C9*-guided warfarin therapy (Caraco et al., 2008), although Veenstra noted that it is somewhat difficult to interpret this study because of the existence of different follow-up periods for the control and study groups. Both studies do give some indication of potential clinical utility, though neither is conclusive. An ongoing trial that may provide more definitive results is the NIH-funded Clarification of Optimal Anticoagulation through Genetics (COAG) trial. The trial will enroll about 1,200 patients and will compare a clinical algorithm versus a clinical-plus-genomic algorithm, assessing the percentage of time that INR is in range in the first month of treatment as the primary outcome.[2] Patients will be

[2] See http://clinicaltrials.gov/ct2/show/NCT00839657.

followed for at least three months and up to one year. Secondary outcomes will include bleeding and clotting events.

There have been several cost-effectiveness studies, Veenstra said. Recent studies have come to the conclusion that there is a great potential for cost savings, but that it cannot be realized until testing costs decrease and the uncertainty concerning effectiveness is reduced (Hughes and Pirmohamed, 2007; Veenstra, 2007; Eckman et al., 2009; Patrick et al., 2009; Meckley et al., 2010).

The Centers for Medicare and Medicaid Services (CMS) recently issued a coverage decision for warfarin pharmacogenomic testing based on the current evidence available. The decision states that CMS will only reimburse testing if the patient is enrolled in a randomized controlled trial with sufficient power to detect major bleeding and thromboembolic events. This is a "coverage with evidence development" approach, Veenstra explained. Likewise, in January 2010 the Food and Drug Administration (FDA) used the information derived from the IWPC report to update the drug label for warfarin to include dose ranges based on pharmacogenomic information. Together, this and a previous label update in 2007 inform healthcare providers about the association between warfarin dosing and variants of the *CYP2C9* and *VKORC1* genes, but they do not require that pharmacogenomic testing be done.

In summary, Veenstra said, there is a validated relationship between warfarin dosing and two different genes. There is a plausible benefit that could be derived from testing, but there are not enough data providing direct evidence of clinical utility. Lastly, the evidence requirements for decision-making are variable and dependant to a certain degree on stakeholder perspective.

PANEL REACTION

Pharmacy Perspective

Anna Garrett, manager of outpatient clinical pharmacy services and a clinical pharmacist practitioner at Mission Hospital in Asheville, North Carolina, discussed her experience managing a large group of patients being treated with warfarin and other injectable agents. About four years ago, Garrett said, sales representatives began talking about genetic testing and warfarin dosing. At that time there was not a lot of evidence to support it, and she noted that she is still of the opinion that there is not enough evidence to suggest that pharmacogenomic testing should change what is being done clinically.

One challenge in an outpatient pharmacy clinic setting is the time it takes to obtain pharmacogenomic test results. If patients are being carefully

managed in a controlled situation, then it will be possible to identify those patients who are highly sensitive to warfarin even before the genomic test results come back, which can be as much as five days after the test is sent out to the laboratory. It is instead the patients who are slow responders to warfarin for whom the genomic information could be of value.

Economics is another concern, Garrett noted. The majority of her patients live in rural areas and are largely on Medicare and cannot pay the $300 to $400 cost of testing. Thus, in order for pharmacogenomic testing to be useful for this patient base, the price would have to drop significantly, she said.

Although such tests are not available, Garret said it would be a real benefit to have genetic testing that could identify those patients who are more likely to have adverse drug interactions (e.g., an exaggerated reaction to warfarin and amiodarone, or an adverse response to the combination of warfarin and acetaminophen or ciprofloxacin). While such reactions are uncommon, they do occur in a subset of patients. As a pharmacist, Garrett said, she finds the prospect of individualized drug therapy based on genetic sequence to be exciting, especially the ability to know which products to treat patients with first, rather than having to try three or four different drugs before finding the one that works best for that patient.

Regulatory Perspective

Elizabeth Mansfield of the Office of In Vitro Diagnostic Devices at the FDA offered firsthand insight into the warfarin label change that Veenstra discussed. The FDA's primary responsibility is the safety and effectiveness of products, Mansfield said. When information becomes available that could potentially reduce adverse events, a timely label change is warranted. An earlier warfarin label change in 2007 told care providers they could use *VKORC1* and *CYP2C9* testing to try to adjust the patient's warfarin dose, but it did not provide any further information, as there was little known at the time. As more data became available, the agency was able to conduct a meta-analysis of a number of studies and derive dose recommendations based on genotype. This is not predictive in any way, Mansfield cautioned, as there are still limited data on outcomes, but the label was changed to provide information to those who felt that they could use it.

Mansfield agreed with Garrett that, while genomic testing could be beneficial in guiding the initial warfarin dose, the testing generally doesn't have a turnaround time fast enough to be useful in this capacity, although some types of point-of-care tests could be envisioned in the near future.

Another focus of Mansfield's office at FDA is the quality of the test being performed. Many of the available genomic tests are laboratory developed and most likely are not reviewed by FDA for their performance char-

acteristics. Of particular concern for genomic testing for warfarin dosing is that before taking warfarin, patients do not express any observable phenotype that would suggest that they have a particular allele of *CYP2C9* or *VKORC1*. Then the patients have one laboratory test done, and the results are assumed to be correct. As such, testing needs to be very accurate, and FDA sets a very high bar for approval—greater than 99 percent accuracy with a 95 percent lower bound confidence interval, Mansfield said. But the FDA can only regulate the tests that it is aware of.

Pharmacogenomic testing, if used, must be used carefully, and in concert with INR, Mansfield concluded.

Private Practice Perspective

Dennis Salisbury, a family physician at the Rocky Mountain Clinic in southwest Montana, addressed how doctors in private practice make the decision whether to recommend pharmacogenomic testing to patients. Reiterating some of the points he made when discussing the Lynch syndrome example, Salisbury said that it is important that there be a clear association between a genomic test and a condition and that there should also be relevant information about the incidence and prevalence of the condition, the severity of the illness's impact, and the potential benefits of the genomic testing. The cost of testing is also a factor. Ultimately, whether to proceed with the testing must be the patient's autonomous decision, but the validity and predictive value of the testing have the greatest weight in determining his recommendations to patients, Salisbury said.

Considering the warfarin example, Salisbury recalled a male patient in his mid 40s who had worked in rice paddies in Southeast Asia most of his life before moving to the United States. The patient had had a valve replacement to address an aortic murmur and aortic insufficiency, and he was sent home, apparently without proper anticoagulation management. He arrived back at a hospital with cardiac tamponade and a prothrombin time greater than 100, which is very high, Salisbury noted. Following pericardiocentesis, the patient developed infective pericarditis and osteomyelitis, and he had to have a muscle flap transposed to hold the bones of his chest together. Salisbury commented that this is a very unfortunate example of what can happen when warfarin is not well managed.

Pharmacogenomic testing for warfarin dosing to patients has some potential benefits, Salisbury said, as well as some potential to improve the way providers manage these patients. Furthermore, the fact that a 2005 report found warfarin to be one of three drugs responsible for one-third of prescription drug-related emergency department visits suggests that there is a potential financial benefit for health systems as well.

Anticoagulation management is challenging for a small practice,

Salisbury said, as it involves calling the patients in, adjusting their dosing, and arranging for another test. Thus, finding a way to make this an easier and more accurate process would also benefit private practice.

Overall, Salisbury said, the data are very exciting and very hopeful, but they do not yet prove that the test is really of value. There are costs to consider besides the cost of the genetic test, he noted. There is a potential for cost savings if INRs could be done less frequently, for example. There are also cost and time savings for patients if they can travel less frequently and miss less work for testing. Finally, there is the cost of the low molecular weight heparin that patients are given during the time when the correct warfarin dose is being determined, which could be reduced if a therapeutic dose is reached sooner. All these costs should be considered when weighing benefits. But right now, Salisbury concluded, the benefit cannot be established, in part, because of the laboratory turnaround time for the test, but also because there are not yet sufficient data to prove cost savings, time savings, or, most important, improvement of outcomes.

Insurance Provider Perspective

Palmetto GBA is a subsidiary of Blue Cross and Blue Shield of South Carolina that provides technology, training, finance, and customer service solutions for health care, including overseeing Medicare benefits. Arthur Lurvey, an endocrinologist and internist and currently a Medicare medical director at Palmetto GBA, provided his perspective on coverage decisions.

Medicare is an insurance plan, Lurvey reminded participants, not a health plan. Medicare pays for the services involved in the diagnosis and treatment of an illness or injury or to repair a damaged organ, but it does not pay for screening, as per the original law. A number of laws passed subsequent to the establishment of Medicare specified additional coverage for colorectal screening, diabetic screening, lipid screening, mammograms, and PSA tests for prostate screening. Pharmacogenomic testing to guide warfarin dosing is different from these cases in that it involves patients with no particular disease, so coverage is not straightforward based on Medicare law. However, Lurvey said, if the government were to decide that testing is related to a particular condition, then perhaps it could be covered under existing precedence. In fact, the test is currently covered when conducted in the context of a randomized, controlled clinical trial.

For the government—and for many of the insurance companies that tend to follow the government—there are two types of coverage, Lurvey explained. National coverage is determined based on a study of all the relevant literature and expert testimony at an open meeting of the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC).

Local coverage is determined by medical directors such as Lurvey, who work with others to determine if Medicare should pay for a particular cost in a particular region when there is no national decision.

In California, for example, there are many individual, small- and medium-sized laboratories that are seeking coverage approval for "home brew" genetic and genomic tests. Since the laboratories conducting these tests are located in California, the "local" coverage decisions are essentially for the whole country, Lurvey said. Unfortunately there are no long-term or even medium-term studies sufficient to guide a coverage decision at this time.

When considering coverage, medical directors review white papers or recommendation guidelines from the relevant specialty societies as well as technical advisory committee reports from Blue Cross and Blue Shield or others, and they talk directly with professors and other academicians in the field. They are not necessarily trying to determine if the test has validity (because most of them do have reproducibility and validity) but rather whether it also has utility. Does it make a difference in either the prognosis of a patient or the treatment path? The other aspect they must consider is cost. While CMS generally does not factor cost into coverage decisions if the test has efficacy, quality, and reproducibility, Lurvey said that a particular concern is that these individual pharmacogenomic tests are going to add a large cost to the system. Everyone will bear the costs through insurance premiums or taxes, he said, whether the tests are paid for by insurance companies or federal or state agencies.

Ultimately, more data are needed on whether these tests have utility and on whether they make a difference in the way that physicians and other providers give treatment or therapy to their patients.

Panel Discussion

Defining Value

Marc Williams, who moderated the discussion, asked the panelists what they look for in determining the value of a test. All the panelists agreed that value encompasses improvements in clinical outcome and quality of life as well as reductions in complications and in morbidity and mortality. Some type of measurable difference in the outcome for the patient is important. Garrett said that a test should provide information that cannot be obtained by other means. Cost is also important, Salisbury added, especially given the number of patients in the community who do not have insurance. Convenience and satisfaction should also be considered. In the case at hand, for example, it would be easier to do an INR test once every 3 weeks than once every 3 days. Lurvey said that prognostic information is very helpful,

particularly if it can guide decisions on whether or not to treat. In assessing value, Veenstra said, evidence-based medicine is key. Representing the FDA view, Mansfield said that the test must also be safe and effective.

Data Collection and Interpretation

Williams noted that it is difficult to translate randomized controlled trial findings into real world clinical practice. Large population-based studies may better reflect what is really happening in practice, but these studies have other issues. Williams asked the panel to comment on how data collection should be balanced in order to better answer the question of value in a timely fashion.

All agreed that no single approach to data collection is sufficient. A challenge in interpreting randomized controlled trials, Veenstra said, is that, for the most part, patients in control groups are not really getting "usual care." They will be receiving high-quality care at an anticoagulation clinic or academic medical center. Evidence arising from real-world trials may be more useful and more generalizable. Garrett concurred, adding that investigators and participants in randomized controlled trials "behave very well" and may not give a good indication of real-world experience versus usual care. Lurvey added that the placebo effect, in which behavior changes because investigators or participants know they are part of a study, also needs to be taken into consideration. While controlled trials do not necessarily represent the real world, Mansfield said, they do give a sense of the potential for what could be achieved if everyone received controlled care. There needs to be a way to determine the potential for a test before looking at the uncontrolled situations in which it is difficult to tease out the variables. Salisbury agreed and suggested that more attention should be paid to practice-based research networks. He also said that the broader use of electronic health records will make it easier to gather data on real care situations and real outcomes. Lurvey suggested that it also might be useful to consider the tremendous amount of claims data that is available.

In terms of the design of trials, Veenstra said, if this test were a drug that had significant potential for revenue, there would have been a lot more invested in its development. Trials of the test have been designed without much information about the optimal design of the intervention. Veenstra and colleagues ran clinical trial simulations and found that elements such as the design of the trial, when dose adjustments are made, and how information on the half-life effect is utilized can modify the effectiveness of the intervention. These are the types of factors that need to be considered when developing a randomized controlled trial. The first step is to define the

questions that really need to be answered in order to have well-designed, adequately powered studies that will generate useful data.

Mansfield noted that the FDA works to ensure that any device being developed is answering a specific question to begin with, which helps guide companies toward defining the intended use of the device. The FDA also has the authority to require post-market studies for devices, but only to the extent of determining safety and efficacy in populations or circumstances beyond the original application. Warfarin is an old drug, and there is limited authority to go back and enforce any changes unless there is a safety issue (which is how the label change was posed). Mansfield said that it would certainly be possible for FDA to work with others to define the key questions and the appropriate trial design, but the agency could not mandate those things.

Genotype Versus Expressed Phenotype

Management at anticoagulation clinics has been shown to improve outcomes in patients that are on anticoagulant medications, but it is not possible to have anticoagulation clinics everywhere, Williams said. Given that, would genotyping be more appropriate in certain settings? Would an inexpensive point-of-care test be of greater value in a rural practice than in a large academic center that can afford to have an anticoagulation clinic? And how do we explore when other types of interventions may be more appropriate than genotypic methods? As an example, Williams noted that home INR monitoring is not available in the United States, but it is done in Europe, and outcomes are much better there.

Veenstra responded that there is a great potential benefit for genetic testing in populations that are rural or underserved, but those are populations that are challenging to study. Epidemiological approaches may help. One question could be, for example, whether someone with a variant *CYP2C9* gene who lives in a rural area, where he or she may not be seen as frequently, is at a higher risk than someone who is seen on a regular basis. Correspondingly, is it better to try to provide such people with genetic testing or with improved anticoagulation services? Garrett agreed that genetic testing would be beneficial for people who are in more rural areas and do not have access to anti-coagulation clinics, especially if it is given in combination with home INR testing, although she noted that this type of change in service would lead to a severe drop in laboratory revenue.

Lurvey said that a fair number of INR tests are still necessary when warfarin therapy is initiated. Genotyping can help to identify a starting level and may indicate if a much higher dose will be needed, but it does not change the amount of testing required. He reminded the panel that the genetic test has to be interpreted and is only helpful if used correctly. Just

making the test available will not necessarily be of much help to providers who do not do such testing very often and do not know how to use it. Mansfield replied that the testing, as described in the warfarin label, can provide some confidence to the physician, helping to guide the physician if the patient has a poor INR.

The study done at Intermountain found that the total number of INRs done in the entire population that was genotyped was, in fact, reduced, and this was factored into the economic analysis, Williams said. One question that has not been addressed is when to draw the INR. Particularly for those with *CYP2C9* variants, when the INR is drawn and when the dosage adjustments are made may have a significant influence on safety. The INR measurement can also be imprecise. A measurement of 3, for example, could be anywhere between about a 3.3 and a 2.7. One problem that was discovered, Williams said, was that if the patient had a 3.1 measurement, a dose adjustment was made to bring it closer to 3. Williams referred to this as "tampering," where a process that is already stable is adjusted. Intermountain then put into effect a process improvement which calls for the dose to remain unchanged but the INR to be measured again a little sooner if the patient is in a 10-percent range on either side of the target range. As a result, the amount of time spent in range increased from 50 percent to 75 percent for the patients in that population.

OPEN DISCUSSION

Electronic Health Records and Data Capture

A participant noted that it is currently very challenging to try to compare data across electronic health record systems because there are no data element standards. Williams said that a provision in the High Tech Act of 2009 calls for meaningful use standards for electronic health records, but it does not recognize the potential that standardized electronic health records could have for research. The 2007 FDAAA addresses post-market data gathering, and the issue of infrastructure, Mansfield said, is at the forefront for both healthcare organizations with electronic health records and also the FDA with its own data management infrastructure. Mining data from electronic health records can help provide a picture of how medicine is really practiced across the country and what care patients are getting, Salisbury said. Lurvey concurred and added that examining claims data allows one to see the existence of marked differences in practice patterns between urban and rural areas as well as across different states.

Williams noted that there are rich amounts of observational information in medical records, but virtually none of it is captured in a structured

or organized way. As such, researchers must resort to working with billing codes or other procedure codes in their search for data. More focus is needed on how to capture this clinic information at a rich level so it can be used not only for the current study but for future analysis as well. Lurvey pointed out that it is difficult to anticipate what data will be of interest in the future. Williams said the goal should be to capture all possible information, but Lurvey said that such an approach would be expensive. Williams responded that data capture and storage are not expensive beyond the original infrastructure costs.

Coverage with Evidence Development

A coverage decision from CMS regarding evidence development directly applies only to the Medicare population. A participant noted that she is working with Aetna, United, and a number of other plans around the country to develop a similar protocol across systems and thus a greater patient population. Currently each plan does its own evidence development and technology assessment, she said, so bringing plans together to develop a unified approach is complicated. With the tremendous pressure on private sector plans to cover genetic tests, this type of wide-ranging coverage decision could produce the evidence required to determine clinical utility.

Payers do pay for coverage with evidence development in children's oncology, Williams said. In essence, every child with cancer in the United States is being treated with experimental protocols. This has had a tremendous impact on the knowledge base about these rare tumors and how best to treat them—an effect that is measurable in terms of outcomes and morbidity and mortality. It is not clear, however, whether such a model could be translated to other areas, such as pharmacogenomics.

Translation into Clinical Practice

A participant mentioned the recent black box warning added to the label for Plavix, which notes that patients with *CYP2C19* variants may not metabolize the drug as expected. There has been a lot of discussion that this might drive an increased use of genetic testing for prescribing Plavix, he said, even though there is an alternative—prasugrel—whose metabolism does not appear to be affected by the same genetic mutation. Would a different standard be applied in a case like this in which there is an alternative, or would the same standard be applied to all pharmacogenetic opportunities? Garrett responded that decisions will probably be on a case-by-case basis. Offering the physician perspective, Salisbury said that he does not anticipate that situations such as the Plavix warning will drive a more gen-

eral adoption of genetic testing; rather, it will drive physicians and other providers toward a product that is easier to prescribe.

Because every case has a different risk–benefit trade-off, Mansfield predicted that decisions will continue to be made on a case-by-case basis. Veenstra agreed, noting that the Plavix case has the potential to change people's perceptions to a certain degree about pharmacogenetic testing. If the warfarin test was for a drug interaction, there would be no question, he said, and testing would be the standard of care. Or if the test cost $5 and the results were available in 5 minutes, it would likely be widely done. There is some point at which the evidence threshold changes, and where that point is will most likely be determined by safety considerations. Another important consideration, Williams added, is how broadly a drug is used. A drug like Warfarin, which may have two million new users each year, will require a different evidentiary standard than a drug for a rare disorder which might be used 100 to 200 times a year.

Lurvey noted that many groups have been urging CMS to make a national decision on genetics and genomics in general. At some point the government may make a decision on payment or coverage for this wide range of tests, but the government won't determine which tests are best.

For this particular case, roundtable chair Burke observed, there is agreement across the panel that there just is no convincing evidence yet. This raises two key questions for the translation of genomic-based research: What evidence is compelling case by case? and, How can that evidence be obtained? Certain kinds of research infrastructures might lead to more efficiency, she said, but ultimately it comes down to who is going to pay for what level of evidence. Given that cost is always a concern in this kind of situation, are there ways to collect quality evidence more efficiently? Burke said that one model might be provided by the development of the Oncotype DX test, a prospective-retrospective approach in which a hypothesis was developed and then addressed using existing specimens from prior randomized controlled trials. We need to think innovatively about evidence in that way and apply it as broadly as we can, she said.

Veenstra suggested that two approaches will come out of the comparative effectiveness research area, one a priority-setting process involving multiple stakeholders providing input on study design and the other a quantitative approach to assessing the potential benefit of the research and the value of the information analyses.

A participant noted that there are different settings in which health care is provided, and different ways that warfarin treatment is initiated (i.e., inpatient versus outpatient initiation, rural versus academic medical center, different indications for warfarin use, and different target INRs depending on the indication). When considering a warfarin genotyping study, which

of those settings should be used, what are the most important questions to answer, and how should those questions be formulated?

Another gap, Williams said, is research around implementation. If something is found to work, how is it then implemented so that it works for everyone? At Intermountain, for example, implementation of Lynch syndrome testing is automated. Tissue from colorectal cancer patients follows a standardized pathway, and ordering Lynch screening is not dependant on any individual care provider. Veenstra added that ideally there would be a generalizable model that can be modular and adaptable because it is not acceptable to wait an average of 17 years from the point when enough evidence is collected to demonstrate clinical utility until the time that a test is fully implemented.

4

Genomic Profiling

For the third clinical scenario, Bruce Blumberg of Kaiser Permanente presented a hypothetical case of direct-to-consumer genetic testing that was designed to raise a variety of issues that occur in real-life cases.[1] Genomic analysis for the prediction of common disease risk is controversial. Proponents support an individual's right of unrestricted access to his or her personal genetic information, while opponents stress the lack of consensus on the genetic markers used in genomic profiling and the inconsistency of risk predictions. In addition to the ethical, legal, and social issues surrounding genomic profiling, questions persist regarding the clinical utility, safety, and cost-effectiveness of genomics-based risk assessment.

GENOMIC SCREENING FOR HEALTH RISK ASSESSMENT

A number of clinical laboratories offer direct-to-consumer genomic profiling either for risk assessment for common diseases or for carrier status for less common Mendelian disorders. Currently, Blumberg said, the three most prominent genomic profiling companies are Navigenics, 23 and Me, and deCODE, and there are ten diseases that all three companies include in their risk assessment panels: age-related macular degeneration, atrial fibrillation, breast cancer, celiac disease, Crohn's disease, prostate cancer, psoriasis, rheumatoid arthritis, type 2 diabetes, and deep vein thrombosis. There are also numerous other diseases that are included in the panels of only one or two of the companies. Examples include Parkinson's disease,

[1] The complete scenario provided to workshop participants is available in Appendix E.

BOX 4-1
Definitions

Association A statistical phenomenon referring to any two events that occur together at a non-random frequency, in this case, two genetically determined characteristics. Association does not imply, nor does it exclude causality. The concept of association was defined long before human genome sequencing began and is also used to describe protein variations and observable physical characteristics.

Single nucleotide polymorphism (SNP) A DNA sequence variation caused by a single nucleotide change. In order to be considered a SNP, the variation must be seen in at least 1 percent of the population. SNPs are very common and occur somewhere between one in every 100 and one in every 300 nucleotides.

Genome-Wide Association Study (GWAS) A study of genetic variation across the entire genome designed to identify genetic associations with observable traits. The primary goal of most GWAS studies is the identification of gene-disease associations.

Alzheimer's disease, lupus, osteoarthritis, multiple sclerosis, lung cancer, kidney stones, gallstones, and gout.

To facilitate the panel discussion of genomic profiling, Blumberg presented the fictional case history of "Anne," who is intended to be representative of the average consumer who might have his or her genome sequenced at a commercial facility. Box 4-1 provides definitions relevant to the discussion.

Anne's Story

Anne is a recently divorced 36-year-old MBA financial analyst. She has always considered herself to be both healthy and health conscious. She is an only child, her mother is of English ancestry, and her father of mixed Eastern European descent. Her past medical history is notable only for a mildly abnormal glucose tolerance test during her second pregnancy at age 31, which was not medically followed after the pregnancy. Anne prides herself on her careful diet, and she runs on a treadmill at her workplace gym at least three times a week. Despite these efforts, she is 15 pounds overweight according to a table that she found in a popular magazine. She has never smoked. She has been tired lately, which may be caused by the demands of juggling single motherhood with a career. Anne's mother is 67 years old and was treated at age 59 for melanoma, but Anne knows no further details. Her mother has recently had mildly elevated blood sugars,

and her doctor is considering oral hypoglycemic therapy. Anne's father is 70 and is taking a statin for hypercholesterolemia and a beta blocker for hypertension. He had a very mild heart attack in his late 40s, and he takes prophylactic aspirin. Two of the father's maternal first cousins are said to have died of colon cancer in their 40s, but, again, no details are available. His paternal aunt died of breast cancer in her late 30s. There may be other relevant conditions in the family history, but no physician has ever asked Anne about this.

Anne has read articles in the *New York Times* and elsewhere about the availability of genomic screening for health risk assessment. As is her usual practice in health-related matters, Anne has extensively reviewed the topic on the Internet and compared the tests offered by several different companies. Based on her personal and family histories, she is especially concerned about her future risk of diabetes and coronary artery disease, so she selects the laboratory that places the greatest emphasis on these conditions on its website, and she submits a sample prior to leaving for a vacation. Upon returning, a printed report awaits her. If she understands the report correctly, she is relieved to learn that her risk for type 2 diabetes is 10 percent below that of the general population. On the other hand, her risk of developing coronary artery disease sometime in the future is 20 percent above that of the general population risk. It is unclear from the report whether the risks have taken her family or personal histories into account or whether the calculated risks are based exclusively on the genomic results. As she continues to read the report, Anne learns that her breast cancer risk is 30 percent above the risk for the general population, and she is dismayed to read that her Alzheimer's disease risk is double the general population risk. Finally, she is surprised and confused when she reads that she is a carrier for hemochromatosis and alpha-1 antitrypsin deficiency, two conditions with which she is entirely unfamiliar. She wonders if these findings might explain her recent fatigue. Anne immediately calls her doctor's office, but the earliest available appointment is in 2 weeks. When she arrives for the appointment with her report in hand, she appears to be mildly agitated.

PANEL REACTION

Genetic Counselor Perspective

Janet Williams, a genetic counselor at Intermountain Healthcare, said that the first challenge in working with a patient like Anne is knowing what the SNP results mean in terms of actual clinical risks in the future. A genetic counselor would look at the family history and deal with known risks, such as cancer, diabetes, and coronary artery disease, and any SNP profile results would be considered in this context and also in the context of what can

be measured clinically. The real difficulty for a counselor is providing the patient with a useful risk estimate that takes all of the relevant risk information into account. Anne is very health conscious and very motivated by the information she has received. She thought she had her lifetime risks well identified, but this profile has opened up an entirely new set of concerns for her, and it has potentially distracted her from other issues that are still appropriate for her to be concerned about, such as the family history of diabetes. At this time, Williams said, there is not enough evidence concerning how to use genomic profiling results to provide useful clinical information for a patient. Thus, counselors are left in the position of not having an appropriate response to the patients' questions and concerns.

Clinical Genetics Perspective

David Witt, a clinical medical geneticist at Kaiser Permanente, said that while he is generally enthusiastic about bringing new discoveries to the clinical setting, he is not enthusiastic about the type of genomic profiling described in the scenario. The case presented illustrates some of the many pitfalls that can occur in screening, demonstrating why it currently has very limited value and in some cases can actually be harmful. Most of the risk estimates that can be obtained today through genomic profiling, Witt said, are so minimally useful that a person does not need to be concerned with them. Furthermore, the reported risks are often already being addressed based on family history information. Witt proceeded to review the profile results in detail and highlighted some of the issues each of the findings creates, especially how the reported risk levels can be confusing and easily misinterpreted and can possibly lead to unnecessary testing or procedures.

Interpretation of the results can pose a significant issue for a patient. Concerning the findings for hemochromatosis and alpha-1 antitrypsin deficiency, the patient has received information that was not sought and which is not understood, as indicated in this case by Anne's lack of a clear understanding of the difference between being a carrier and having an expressed condition. This led Anne to seek counseling from her primary care physician, thus taking up the provider's time to explain the results, assuming that the provider is capable of doing so, Witt said. Furthermore, the screening results have created unnecessary anxiety about something that may have limited personal or familial value.

Another important thing to consider, Witt said, is that the risks presented are based on the current markers that the individual laboratory has selected to test, but as more and more markers related to chronic diseases such as diabetes and heart disease are found, the results today could be modified in the future to indicate either a higher or lower risk or else could be invalidated altogether. Furthermore, how the testing company

presents the results can have a significant effect on the patient's perception. The percent risk scores given for diabetes (10 percent lower), coronary artery disease (20 percent higher), breast cancer (30 percent higher), and Alzheimer's disease (double) actually represent very small differences in actual numerical risk. For diabetes, this patient's risk compared to the general population decreases from 5 to 4.5 percent, and for breast cancer has increased from 10 to 13 percent. None of these changes are overwhelming, Witt said, and they should not override any of the current recommendations for standard of care or for practices based on family history. An argument could be made that a patient perceiving a higher risk would be inspired to do more preventative practices, such as increased breast exams, but the misunderstanding about what the presented risk scores mean could cause significant emotional distress or lead to a demand for screening tests that are not warranted, Witt said. Additionally, there may be little positive value in identifying an increased risk for a disease such as Alzheimer's, for which there are currently no options for screening or intervention.

Witt questioned what information of real consequential value Anne received for the $500 or $2,500 she spent for the genomic profiling. She received some risk figures that she does not understand and which are perceived as being more substantial than they really are. These results won't translate into any significant change in her healthcare management, nor will they have any practical consequences that will significantly influence her overall health in terms of quality of life or duration. At the same time, however, these results have created significant anxiety for her, and they have an additional cost in terms of the healthcare provider's time. Finally, there is the danger of an uninformed or inexperienced provider advocating that Anne or her relatives receive additional genomic testing.

Public Perspective

Karen Kaplan, a science reporter for the *Los Angeles Times*, provided perspective on the public understanding of genomic profiling. The SNPs that are being used were identified in a GWAS study and turned into a commercial product, she said. Kaplan agreed with Witt's analysis that these profiles don't provide meaningful information about personal health. Additionally, a lot of consumers who are thinking about having a genomic profile done do not consider whether a test has been FDA approved. Often, just the fact that something is expensive causes some people to believe it is legitimate.

Kaplan mentioned that there have been commentaries published in the *New England Journal of Medicine*, *JAMA*, and other medical journals advising physicians what to do if they find themselves faced with this type of scenario. Most physicians do not receive extensive genetics training in

medical school, and many are just as confused as the patient about how to deal with these test results. The advice that is routinely given in these journals is to explain to the patient why he or she should ignore the results and to say that they do not supersede anything the patient already knows from family or personal medical histories. Kaplan speculated that as the cost comes down, more people will have genomic profiling done. There have been efforts to present it as a "fun" thing to do—spend a few hundred dollars and compare your SNPs to your friend's SNPs. The attitude has been "What could be the harm?" The harm, Witt said, is that people might discover something completely unexpected that they are not prepared to deal with. Individuals who approach this seriously should talk to a genetic counselor before they begin the process, Kaplan advised.

Preventive Services Perspective

Steven Woolf, a professor in the departments of family medicine, epidemiology, and community health at Virginia Commonwealth University and a family physician with a background in the evidence-based evaluation of screening tests, suggested that the roundtable should consider the issues of genomic profiling within the established frameworks for evaluating screening tests. Regardless of the type of test, he said, there is a standard set of analytic principles that are routinely applied when evaluating screening tests. Groups such as the U.S. Preventive Services Task Force and the World Health Organization generally consider five issues when assessing preventative interventions: (1) the burden of suffering from the target condition; (2) the accuracy and reliability of the test; (3) the effectiveness of early detection of the condition; (4) potential harms; and (5) the balance of benefits and harms (USPSTF, 1996). Most of what has been discussed thus far at the workshop fits into these categories, Woolf said.

The burden of suffering from the target condition is relevant because many of the diseases for which there are genomic tests are inherently serious. With regard to the accuracy and reliability of the tests, Woolf said that one should consider sensitivity, specificity, and positive predictive value. According to fundamental Bayesian statistical principles, if the condition has a low prevalence, even a test with very high sensitivity and specificity can produce a very high proportion of false positive results. Thus, there can be a very low positive predictive value even with a highly accurate test, if applied to a condition with low probability. This is important to consider for some of the conditions reviewed at the workshop, Woolf said.

One should also carefully scrutinize the reproducibility and predictive properties of genomic tests in terms of the precision with which they predict the future development of a disease. Woolf mentioned the Bonferroni correction, a statistical method employed when considering a test that looks

at multiple parameters. For example, the probability of producing erroneous or spurious information is statistically increased when multiple tests are done together (as occurs in a chemistry panel or whole body imaging). Woolf questioned whether this concept might be applicable to genomic profiling as well.

Is there a benefit to early detection of the particular condition? There has been a perception in society and in the medical community that knowing one has a disease or a risk for a disease has inherent benefits, regardless of whether the testing actually leads to improved health outcomes. However to be considered clinically effective, a screening test must improve the likelihood of positive health outcomes. Evidence of an association does not necessarily imply that there is a benefit that can be employed. Optimal study design, modeling, and the role of intermediate health outcomes as opposed to distal health outcomes should all be considered when assessing the effectiveness of a test. Relative versus absolute benefit is very important to consider, Woolf said, as is efficacy versus effectiveness. (Efficacy is the performance under ideal conditions and effectiveness is how well the test performs in real-world settings.)

When considering harms, one should include both the immediate harms of the test experience itself and the harms of the downstream cascade that may be set in motion by the test results (ranging from patient anxiety to the distal effects on employers and insurance eligibility). Potential harms also include false reassurance (e.g., a patient might decide she does not need to keep using the treadmill three times a week because of a particular test result) and false resignation (she might conclude, based on the test results, that there is nothing she can do to prevent the inevitable occurrence of disease). Costs are sometimes considered as part of the harms, but Woolf noted that there is some controversy as to whether they should be.

Finally, the balance of benefits and harms is complicated. The typical advice is that the clinician and patient should work together to review benefits and harms and consider personal preferences, and together they should make the choice that is best for the patient, as is done in genetic counseling. Unfortunately, with direct marketing of genomic profiling to the public, that collaborative decision-making process is bypassed and the consumer is exposed to these tests without that benefit.

Woolf pointed out that many of the fundamental issues raised during the workshop discussion apply broadly to all areas of medicine. For example, the need for infrastructure for improving the quality of care (e.g., anticoagulation clinics) is something being dealt with throughout medicine. The need for faster, real-world research on effectiveness, the idea of practice-based research networks, and the use of other venues for collecting real-world data are all being studied in health services research across many topics. Nor is the need for helping patients to make better choices

about complicated trade-offs unique to genomics. These are system redesign issues that are very important for health care, and they will certainly benefit genomics, but they need to be dealt with generically in medicine and are not necessarily specific to this particular topic.

Commercial Genomics Perspective

Vance Vanier, CEO and president of Navigenics, said that more than 98 percent of the company's business comes from national physician groups and medical directors of large self-insured employers. An in-house team of genetic counselors is available for both pretest counseling and, for 1 year afterward, for post-test counseling. To date, only a small subset of possible conditions that are deemed clinically actionable are available in the profile. The business is now regulated under the state versions of the Clinical Laboratory Improvement Amendments (CLIA), and Navigenics is currently the only company offering these tests to be approved in all 50 states. Navigenics does not test minors, Vanier said, and patients receive updates relevant to their genome so that they can take advantage of new discoveries.

Vanier said that when the company first launched its genomic profile product, it was popular for reporters to be tested, to speak with one of the genetic counselors, and then to write about their experience. He recalled one particular reporter who was homozygous for every marker included in the screen for macular degeneration, which increased her risk by a factor of between 5 and 10. However she was more interested in the fact that her risk of Crohn's disease was 0.1 percent higher than normal. When questioned if she had any concern about the macular degeneration risk, she responded that she had talked with her doctor and he had told her to eat more spinach, so she was comfortable with that result. Later she mentioned that her sister has Crohn's disease, so that was much more emotionally meaningful for her, and she interpreted the Crohn's risk very differently than a physician or a genetic counselor would.

There are some who are of the opinion that it is "paternalistic" to assume that physician involvement is needed and who argue that if people can understand baseball statistics they should be able to understand genetics statistics. Navigenics is not of that opinion, Vanier said, stressing that physician involvement in genomic testing is extremely important, particularly physician education and medical alignment with regard to such testing. Overselling the usefulness of the genetic testing in this early period would be extremely detrimental, Vanier said. The question that needs to be addressed is how to navigate the course to the distant future when genomics will provide the preventative measures it has the potential for.

Behavioral change, Vanier said, is one outcome of genomic profiling that is frequently overlooked. Emerging data suggest that showing people

their genetic profiles is motivating and can compel them to do all the healthy things that physicians have been telling them to do for years but that they never do (e.g., exercise, diet, medical compliance). There are some who believe that if genomic profiling even slightly increases patient compliance and positive behavioral change, it will have been of enormous value to society, regardless of how the screening question plays out.

In terms of evidence of clinical utility, genomics screening is no different than PSA testing or mammograms in that it will take a long time to prove its value. Clearly, genetic profiling is not a substitute for family history, but family history has its own limitations as a screening tool. How often, for example, do people really know what their grandparents died of? How often do physicians in the average office encounter manage to get a good family history? As we move toward the future, Vanier said, we will need to look for the small proof points and small focused areas of utility along the way that can make a difference and that can accelerate the adoption of genomics in a clinically useful manner.

Panel Discussion

Cost and Value

Marc Williams, moderating the discussion, noted that the cost of genotyping is rapidly dropping to the point where whole genomes can be sequenced as cheaply as, if not more cheaply than, single genes. How do we balance the desire to achieve economies of scale with the potential for downstream costs associated with obtaining volumes of information that really are not needed or even understood yet?

Woolf answered that the potential for economies of scale to make profiling more broadly affordable compounds his concerns about the potential misinformation that could be generated. The bottom line is whether there is evidence that performing a test is going to make people healthier. Woolf said that he supports research to collect that evidence, but as a policy matter, until the evidentiary threshold is reached, it is premature to advocate such consumer-oriented genomic tests, whether in isolation or as inexpensive sets that invoke economies of scale.

In some cases, Vanier said, the price that a consumer pays out of pocket for a bundled test is now less than what the laboratory would charge through a traditional third-party reimbursement system for a single indication. The cost of genotyping is coming down at such a brisk rate that within the next 12 to 24 months, for the same cost that one could obtain pharmacogenomic information for use in warfarin dosing, one could sequence an entire genome and at least acquire a dozen other pharmacogenomic indicators as well. Given the concerns raised with waiting five

days to get warfain pharmacogenomic results back from the laboratory, he asked, would it not be better to have all of the pharmacogenomic markers available in the electronic medical record, ready for when the physician has another drug to prescribe? Janet Williams responded that this assumes a level of data retrieval and cross talk between electronic medical record systems, laboratory systems, and pharmaceutical entry systems that does not exist right now.

Even if genome sequencing were free and entire genomes were decoded at birth and stored on a medical ID bracelet, Kaplan asked, what is the most that that could tell you? Genomic sequence data do not take into account epigenetics, environmental influences, or numerous other inputs. It is very easy for consumers to buy into the idea that if it is in their DNA then it must be real, but there is a big gap remaining between information and meaning. We can bridge the cost gap, Kaplan said, but what are the possibilities for bridging the information gap?

Data Collection and Analysis

One unusual characteristic of genetics and genomics, Marc Williams said, is that there is no currently available standard for representation of genetic or genomic information in any of the available electronic health records or personal health records. Information is stored as text entries. To be actionable, these entries will need to be computable—for example, to be able to be entered into decision support algorithms. This is an infrastructure gap that is not currently being addressed, and it may be unique to genetics and genomics. Another challenge, Vanier said, is having a system where that baseline information can be acquired cost effectively, entered, and then continually made use of as understanding evolves.

Risk Assessment

Witt noted that many of the SNPs in use today for drawing conclusions about risk may not give accurate assessments. Perhaps if another thousand SNPs were added and assessed, there would be a different risk finding. Witt described a recent study in which specimens from five individuals were sent to two genomic profiling labs. While there was great overlap in terms of analytic validity (i.e., similar results in terms of SNPs), the risk assessments differed about two-thirds of the time, even as to whether the risk was decreased or increased. This is evidence, Witt said, that genomic profiling is not ready for public consumption.

Vanier agreed that there have been many examples showing that the same sample tested at the three major companies may receive different risk factors. While the analytic validity is good across all three companies

because everyone is using a CLIA lab, the different companies are using different marker selections, he said, which results in different risk scores. This reflects different philosophies among the companies in how they pick the specific markers. The Centers for Disease Control and Prevention estimates that only 7 percent of the markers identified are ready for use in screening. Whether through regulation or self-policing, the industry as a whole needs to do a better job defining a more conservative base of markers to be used. Unfortunately, whether in genomics or existing clinical care, whether in an academic or community setting, there will always be a breadth of standard of care. Thus it is very important, in the early years of a field like this, for patients to approach the task in partnership with the medical community.

Individual Benefits/Personal Utility

As the author of the hypothetical case scenario, Blumberg speculated further that maybe seeing her increased risk for coronary artery disease in her genomic profile was the stimulus that finally prompted Anne to lose 15 pounds and that in the end, after her visit with her doctor, she has no regrets and would do it over again, finding value in the information obtained. So, considering Anne's story as that of one individual, and not in terms of a broad screening program, Blumberg asked if denying her that opportunity or steering her away from it during a consultation prior to testing would have been paternalistic. Witt repeated his earlier comment that if Anne's small increase in breast cancer risk leads her to do more self-exams on a regular basis or to go see a provider, then, to that extent, screening has had a positive effect. But looking beyond the individual patient, as a provider in a system that provides care to over 3 million people, he said that the public health perspective must be considered also. In any individual case, it could be argued that there could be some benefit. But looking at the big picture, he said, the benefits are not there. Witt speculated that most people will not take any action based on the results and said the costs are still prohibitive. He also questioned the quality of the counseling in some of the companies.

Further discussing behavioral change, Woolf said that obesity and smoking are common not because people lack motivation or because they do not know that being overweight or smoking is unhealthy. Any sophisticated understanding of why these unhealthy behaviors are so prevalent has to take into account various environmental and contextual factors. Thus, although motivation gained from a genetic test may be of some benefit, the real opportunities for changing health behaviors are associated with the natural, built, and social environments (e.g., living conditions, dietary habits, availability of safe areas to walk, and advertising). Vanier agreed, adding that genetics tests should be bundled in a suite of services that

include messages advocating a healthy lifestyle, health coaching, and other follow-on activities. The teachable moment is when the individual first sees his or her results.

Marc Williams said that geneticists have historically had very little to offer in the way of treatment, and yet they have still been advocates for testing in many situations. In a study of Huntington's disease, for example, a selected cohort of individuals who had been screened had an overall self-reported anxiety score and self-perceived sense of health that were much closer to normal than those individuals who had chosen not to be tested, irrespective of whether the screening showed that the subject carried the mutation. In the insurance world, the single greatest predictor for healthcare expenditures is self-perceived health. One could argue that if, in fact, this testing led individuals to be less anxious and to have a better self-perceived health, that might then reduce expenditures. Is it possible to quantify personal utility? Witt noted that predictive testing for Huntington's disease is different from many other genetic tests in that the results are not going to lead to any medical intervention or health test. The value lies simply with providing information for the person and, even in the absence of useful treatment, having this information can be of great value to people. There is a significant difference between predictive testing for Huntington's disease and broad genomic profiling. Vanier noted that in the REVEAL study (Risk Evaluation and Education for Alzheimer's Disease) the most interesting use of the individual risk information derived from the test was for use in financial planning.

OPEN DISCUSSION

Public and Professional Understanding of Genomics

One participant said that genomic profiling should not be prohibited, but rather should be used to increase medical knowledge and health awareness through patient education and continuing medical education for professionals. The participant also pointed to the sophistication of social network groups of patients who do understand genomics and who can manage their chronic diseases better because they seek out the best treatment and can understand scientific evidence. Witt agreed that there needs to be education but expressed concern that consumers of genomic testing are being thrust into this situation and their doctors may not be up to speed. The participant responded that the marketplace for genomic profiling is still small and that the medical profession has an opportunity to catch up and get ahead. Genomics should be in more medical school curriculums and addressed in residencies as well. The participant urged the medical profession not to underestimate patients' ability to understand genomics. Vanier added that the Navigenics genetic counseling team spends about 45 percent of their time with the

physicians the company works with. Often a physician will call the genetic counselor to make sure he or she understands all the issues before seeing the patient face to face and providing the genetic results. Physicians usually do that for the first 10 to 15 tests they order, he said. There are clearly lessons to be learned, Marc Williams added, about how to communicate risk information more effectively to all stakeholders.

Costs

Marc Williams pointed out that while genomic profiling is currently paid out-of-pocket by consumers, there could be costs and consequences associated with the medical interventions that would take place as a result of the findings. He referred to the example of Jeffrey Gulcher of DeCODE who had his profile done and identified an increased risk for prostate cancer. A subsequent biopsy confirmed that Gulcher did indeed have prostate cancer, and he began treatments. From a personal utility perspective, this is an outstanding result, Williams said. But if every individual who received a similar risk result followed suit and went for biopsy, the consequences in terms of cost to health systems and payers—and potentially the patient—would be significant.

Benefits and Harms

Roundtable chair Burke observed that there was general agreement among the panel that there is insufficient evidence at this point to claim clinical benefit from personal genomics and that there may be reason to be concerned about potential harms, such as cascade effects, false positive results, false reassurance, or about relatively trivial risks taking up practitioners' time. As research is done to understand the effects of genomic profiling, she asked, shouldn't there also be an effort to understand how to avoid harm? And how would such studies be designed? Absent the evidence of benefit, should practitioners be recommending against screening—not just a neutral position, but actually a negative recommendation?

Woolf responded that an empirical basis would be needed for any negative recommendation as well. There must be reasonably good evidence of harms to make the case that the harms outweigh the benefits. He agreed that studies need to be designed to be inclusive in terms of outcome measures that look at both benefits and harms (e.g., motivation to adopt healthier behaviors or an adverse chain of events).

Liability

A participant pointed out that FDA, CLIA, the courts, and the court of public approval will all factor into this new era of disease-gene association and that there will be liability issues to address. He offered the innovative biotechnology industry as an analogy. A biotechnology company is supported by investors and dependent on the public buying its product. If the company gets it wrong (e.g., produces a faulty product that causes harms or does not work), its board will vote to close the company down because it failed and is not making money. Checks and balances also occur out in the marketplace where consumers vote with their dollars. The participant said that it is fine to be ahead of the field, whether in biotechnology or in genomic testing, but one should keep in mind that he will be held accountable by investors and consumers, by regulators, and by the courts.

The Evolution of Technology and Data

A participant suggested that the era of SNPs is dead since they provide such a small amount of information and that we are quickly moving to full genomic sequencing. The participant asked whether it is even worthwhile to continue discussing how to use SNPs. Marc Williams responded that the fundamental issues are more concerned with managing the information than with any specific technology. Making things clinically relevant is not dependent on whatever the technology currently being used is but rather on the level of confidence there is in the technology's predictive value and if that information is actionable.

This is one of the challenges, Blumberg added, when traditional methods of evidence generation are so much slower than the advance of technology and technological methodology. Perhaps by the time that the current warfarin clinical studies produce results in 2012, another gene may have been identified that, when added to the protocol, makes the difference between clinical utility and nonclinical utility. The old method of one test at a time, one protocol at a time, one disease at a time, is at odds with the profusion of new data and technology that is now available.

Vanier said that this is an evolving process. The algorithms and infrastructure it takes to translate SNP information into an end use are not unlike those that would be used for targeted sequencing and which could then be adapted to whole genome sequencing. The obvious difference is the volume of data that will be put through that infrastructure. SNPs are a first step toward mass utility whole genome sequencing, he said.

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Closing Remarks

The roundtable chair, Wylie Burke, reiterated that the workshop was held to gain a better understanding of the diverse perspectives that different stakeholders have regarding the value of genetic testing. Catherine Wicklund, lead member of the workshop planning committee, said that the original plan for the workshop was to discuss implementation: Beginning with the assumption that all of these genomic tests have value, how can they actually be implemented? But from discussions at the previous meeting of the roundtable it became clear that the concept of value needed to be better understood first. As such, three diverse genomic scenarios were chosen for this workshop to serve as the basis for a discussion of the subtle differences between different types of tests and to help participants look for common aspects that are valued.

Burke called upon the case scenario presenters and the participants to share their thoughts on take-home messages of the day and to offer questions for further consideration by the roundtable.

RESEARCH SYSTEMS

A participant noted that one recurring theme was the absence of a suitable research infrastructure for obtaining the necessary data needed to answer some of the questions raised. A related message was that the type of technology currently being employed for genomic profiling is a separate issue from the information and lessons one can learn from genomic profiling. For example, debating the clinical utility of SNP profiling is irrelevant

because it is still not known whether there is clinical validity. The discussion should be focused on how to push a technique through to utility once it has been shown to have clinical validity.

Marc Williams, who presented the Lynch syndrome case scenario (Chapter 2), agreed with the need to build an infrastructure so that some of the questions can be more efficiently answered. He noted that the infrastructure of the Intermountain system is useful in this regard. The company's approach thus far has been very pragmatic, culling through the list of things that are potentially available and investing time and effort on those things that, from the company's perspective, would return value for Intermountain patients.

Bruce Blumberg, who presented the genomic profiling scenario (Chapter 4), agreed that there is a problem with the current paradigm for evidence generation. Technology is advancing more rapidly than our evidentiary approach is able to keep up with. The one-disease-at-a-time, one-test-at-a-time, one-SNP-at-a-time approach to research is no longer viable.

Wicklund noted that funding for research is another important issue. Blumberg said that people tend to be more engaged in something when they have an investment in it. He recommended determining who will benefit from the evidence generation and then asking them to underwrite at least part of the cost of the research. Because they are invested in the process, they will be more likely to follow through in adopting and implementing any recommendations that come out of the studies.

HOW MUCH DATA ARE ENOUGH?

Blumberg returned to the question of "When is enough, enough?" that was raised relative to Lynch syndrome testing, and he asked it of pharmacogenomic testing for warfarin dosing. There is already enough evidence, he said, to conclude that there is no major benefit from genomic testing versus current modes of coagulation management in well-managed clinics. When the effect that is being studied is small, more evidence is needed, and larger and longer studies must be done. When will we be convinced that there is—or is not—some small benefit of genomic testing? If there is such a benefit, decisions should be made based on the needs in each individual clinical setting. For example, genomic testing for warfarin sensitivity may not add value in a well-managed coagulation clinic, but it may be helpful in other settings.

Marc Williams added that too often, not just in genetics but in medicine in general, the approach to problem solving is to assemble panels of experts and "think problems to death." One can always construct worst-case scenarios, he said, but when ideas are implemented, it is rare for those worst-case scenarios to occur. The best-case scenario may not occur either,

but medical practice cannot become paralyzed by the idea that everything must be analyzed and must be exactly right before it can be used. There must be protected harbors where we can learn what is wrong, rapidly make it right, and determine how to apply it. This is how we will learn where the value lies.

PERSONAL VERSUS CLINICAL UTILITY

Clinical practice resides at the intersection of public health and personal health, Blumberg said. Physicians are responsible for the welfare of the individual patient who is before them, but at the same time that patient is part of a population, and management of that patient has implications for the entire population. Taking that approach, if a patient asks for and is given a test that has some benefit, then every patient in the practice population who might benefit from that test ought to be proactively offered the same test. Blumberg observed, however, that especially in the genomic profiling case there is a disconnect between public health and personal health. Some tests that have not been demonstrated to have clinical utility clearly have personal utility. On the individual level it would be paternalistic to presume to know what is in the person's best interest. It is much easier to determine what is in the best interest of the public. How then, Blumberg asked, can personalized care or personalized service be scaled up to an entire population?

Along the same lines, Williams said, is the question of how providers can do a better job of delivering in that short 15-minute appointment what the patient really wants when there is not enough time to deliver all of the preventive messages. Is it possible to identify those patients who are ready to change and target their visits to focus on those areas where there is a high likelihood of behavioral change? If a patient arrives with genomic profiling results in hand and a list of concerns, that is a teachable moment. A physician should not spend time debating whether this SNP is valid or that SNP is not. The physician should instead focus on the patient's concerns and talk about what is known and what can be done. This customizes the visit for that individual patient based on what he or she wants to do at that particular time. To some degree, Williams said, physicians have always done that, but in a very crude way.

Wicklund said that, because she was coming from a pre-natal clinical setting, she expected that there will be companies offering panels of over one hundred different single gene tests to determine carrier status. The cost might be less for a panel of 100 than for a single genetic test for cystic fibrosis or spinal muscular atrophy. How does one balance value in that situation?

If one's goal is to achieve clinical utility, a participant suggested, there are three steps that can be taken to achieve normative change. First, the

physician should recognize that an opportunity has presented itself and should take advantage of that opportunity. If the patient wants to give up smoking or complains about being overweight, the physician should seize that opportunity for intervention. Evidence shows that when a physician recommends a change, the patient is more likely to go through a change. If the physician is not responsive, the patient is less likely to take any action. Second, a physician does not need to be directly involved in areas where he or she does not have expertise and instead should have a referral ready for the patient (e.g., a family planning facility, a drug abuse clinic, a tobacco program, or 1-800 numbers and state-run hotlines). Third, physicians should join an outside group that addresses at least one of these issues in order to help keep the issue alive. This is a responsibility we have as practitioners, the participant said. In summary, take advantage of opportunities with patients, send them to places where they can get help, and be a part of the wider community that addresses at least one of those risks.

ROUNDTABLE ACTIVITIES

Williams' advice to the roundtable was to go forward with the implementation workshop that Wicklund said had been originally intended and to invite groups that have actually implemented some of these genomic tests. These groups have had to consider many of the issues raised over the course of this workshop, and while the answers and solutions they have come up with may be locally oriented, they can offer an array of perspectives on what has been successful and what has been less so.

In all of the cases that were presented, a participant said, a collaborative healthcare delivery model could be an important component of success. She suggested that the roundtable could, as part of the implementation discussion, look to other areas of medicine for models of successful collaborative delivery that could be applied to genomics.

A participant observed that overlaps and redundancies exist in some of the activities of the various stakeholders at the workshop. He suggested that the roundtable consider whether the creation of a genetics and genomics research network would be helpful. This would be a body focused on overarching strategy and coordination, somewhat similar to the HMO Research Network, so that it would not lead to an excess of parallel activity but rather a synergy of efforts.

Burke responded that the emerging Genomics Applications in Practice and Prevention Network (GAPPNet)[1] has some of those goals, and that the roundtable has discussed the need to coordinate activities with GAPPNet.

[1] See http://www.cdc.gov/genomics/translation/GAPPNet/index.htm.

CHAIR'S SUMMARY

Burke said that throughout the workshop she had heard a wide range of optimism and pessimism about the potential benefits of different applications of genomic information in health care. There seems to be agreement that data on outcomes are needed, specifically about benefits and harms. But there is perhaps less agreement as to whether that data can come from practice (implementing potentially beneficial applications) or whether specific measures, actions, or research programs need to be undertaken in order to acquire the evidence. Some of the barriers to data collection that were cited include lack of motivation, lack of funding, and inadequate infrastructure.

In addition to questions about how the data should be obtained, there may also be underlying differences of opinion regarding what types of evidence are most important. These are issues that could be explored using the convening function of the roundtable, Burke suggested. As was noted during the workshop, many of these challenges are not exclusive to genetics, but rather are core issues for health care as a whole (e.g., effectiveness versus efficacy data, building efficient research infrastructures, and randomized controlled trials versus other types of evidence). What, if any, are the specific challenges involved with accumulating data about genomics?

Also noted during the workshop was the fact that there are established analytic approaches for evaluating screening tests that have not yet been applied to genomic tests. Personal genomics currently is not considered a screening model, Burke said, but rather a direct-to-consumer model in which people choose whether or not they want the information. But the underlying health model is, in fact, a screening model. One would screen for risks in people that do not currently have a problem in order to take action to improve the ultimate health outcome. Knowledge from other screening venues should be taken into account and included in the conversation about genome-derived evidence.

Another major topic was clinical utility versus personal utility, and Burke said it might also be important to consider clinical use versus personal use. That is, what genomic information should be used by the healthcare sector in order to accomplish the traditional goals of that sector, and what uses of genetic information are legitimate draws on the resources available for healthcare? There may be reasonable personal uses of genomic information that are not appropriate for bringing into the healthcare setting, and these would be considered consumer-oriented tests. As we address the evidence questions, Burke said, should these two different uses be considered separately? Is it possible to consider them separately? When considering clinical use, it is important to have evidence of a health outcome benefit. In contrast, when considering a test for personal use, the focus may be more on potential harms associated with use, as is the case with other consumer products.

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Appendix A

Workshop Agenda

The Value of Genetic and Genomic Technologies

The Beckman Center of the National Academies
100 Academy
Irvine, CA

March 22, 2010

MEETING OBJECTIVE

To examine the perceived value of genetic and genomic technologies, both present and future, in clinical practice

- How do different stakeholders define the value of genetic and genomic technologies?
- How do stakeholders evaluate the weight of one kind of value in relation to another?
- How do people assess relative values to make health care decisions?
- How do these types of values relate, or not relate, to the monetary cost of the technologies?

8:00–8:15 A.M.	**PUBLIC WORKSHOP BEGINS—AUDITORIUM**
8:00–8:15 A.M.	**Welcome and Introductory Remarks** *Wylie Burke, Roundtable Chair and Professor and Chair of the Department of Bioethics and Humanities, University of Washington*

8:15–10:15 A.M.	**CORRELATION BETWEEN LYNCH SYNDROME AND COLON CANCER**
8:15–8:30 A.M.	**Case Study Presentation** *Marc Williams, Director, Intermountain Healthcare Clinical Genetics Institute, LDS Hospital*
8:30–9:00 A.M.	**Lynch Syndrome Panelists** *Mark Boguski, Associate Professor, Center for Biomedical Informatics, Harvard Medical School* *Roy Gandolfi, Associate Medical Director, SelectHealth* *Don Lyman, Chief, Chronic Disease and Injury Control Division, California Department of Public Health* *Dennis Salisbury, Family Practice Physician, Rocky Mountain Clinic, Butte, MT* *Andrew Spiegel, CEO, Colon Cancer Alliance*
9:00–9:45 A.M.	**Panel discussion**
9:45–10:15 A.M.	**Roundtable discussion**
10:15–10:30 A.M.	**BREAK**
10:30–12:30 P.M.	**PHARMACOGENOMIC TESTING FOR WARFARIN DOSING**
10:30–10:45 A.M.	**Case Study Presentation** *David Veenstra, Associate Professor, Pharmaceutical Outcomes Research and Policy Program and Institute for Public Health Genetics, University of Washington*
10:45–11:15 A.M.	**Warfarin Panelists** *Anna Garrett, Manager, Outpatient Clinical Pharmacy Programs, Mission Hospital, Asheville, NC*

Arthur Lurvey, Medical Director, Palmetto GBA
Elizabeth Mansfield, Director of the Personalized Medicine Staff, Office of In Vitro Diagnostic Devices, Center for Devices and Radiological Health, FDA
Dennis Salisbury, Family Practice Physician, Rocky Mountain Clinic, Butte, MT

11:15 A.M.–12:00 P.M. **Panel discussion**

12:00–12:30 P.M. **Roundtable discussion**

12:30–1:30 P.M. LUNCH

1:30–4:00 P.M. GENOMIC PROFILING

1:30–1:45 P.M. **Case Study Presentation**
Bruce Blumberg, Co-Chief of Medical Genetics, Kaiser Permanente, Oakland and Institutional Director of Graduate Medical Education, Northern California Kaiser Permanente, The Permanente Medical Group

1:45–2:15 P.M. **Genomic Profiling Panelists**
Karen Kaplan, Science Writer, Los Angeles Times
Vance Vanier, CEO and President, Navigenics
Janet Williams, Genetic Counselor, Intermountain Healthcare, Oncology Clinics
David Witt, Genetics Department, Kaiser San Jose Medical Center
Steven Woolf, Professor, Departments of Family Medicine, Epidemiology, and Community Health, Virginia Commonwealth University

2:15–3:15 P.M. **Panel discussion**

3:15–4:00 P.M.	**Roundtable discussion**
4:00–5:00 P.M.	**SUMMARY**
4:00–5:00 P.M.	**Summary and wrap-up discussion** *Bruce Blumberg, Co-Chief of Medical Genetics, Kaiser Permanente, Oakland and Institutional Director of Graduate Medical Education, Northern California Kaiser Permanente, The Permanente Medical Group* *Wylie Burke, Roundtable Chair and Professor and Chair of the Department of Bioethics and Humanities, University of Washington* *Catherine A. Wicklund, Director of the Graduate Program in Genetic Counseling and Assistant Professor, Department of Obstetrics and Gynecology, Northwestern University* *Marc Williams, Director, Intermountain Healthcare Clinical Genetics Institute, LDS Hospital*
5:00 P.M.	**ADJOURN**

Appendix B

Speaker Biographical Sketches

Bruce D. Blumberg, M.D., is director of graduate medical education (the resident physician training programs) for Northern California Kaiser Permanente and has been the Co-Chief of Genetics at the Oakland KP Medical Center, since joining Kaiser Permanente in 1981. He currently maintains small clinical practices at both his Oakland and San Francisco facilities. He believes in a team-based approach to medical care with patients and their families as key members of the team. Since he practices at multiple sites, genetic counselors are a crucial and consistent communication link between him and his patients. Also, he is a clinical professor of pediatrics at the University of California at San Francisco and an adjunct clinical professor of pediatrics at Stanford University School of Medicine. His clinical interests within genetics are broad, and he has a subspecialty interest in inherited disorders of skeletal and connective tissue development. His research interests are in the area of the psychosocial and emotional aspects of prenatal diagnosis. Dr. Blumberg holds a medical degree from Yale University School of Medicine, has completed his residency in pediatrics at Stanford University Hospital and UCLA Center for the Health Sciences, and finished a specialty fellowship in medical genetics at Harbor-UCLA Medical Center. He also received a B.A. from Dartmouth College.

Mark S. Boguski, M.D., Ph.D., is on the faculty of Harvard Medical School at the Center for Biomedical Informatics and the Department of Pathology at Beth Israel Deaconess Medical Center in Boston. He has previously held positions at the Johns Hopkins University School of Medicine, the U.S. National Institutes of Health, and the U.S. National Library of Medicine

and has served as an executive in the biotechnology and pharmaceutical industries. Dr. Boguski is a former vice president of Novartis and was honored as a visionary and influencer by the Personalized Medicine Coalition in 2006. He was elected to the Institute of Medicine of the U.S. National Academy of Sciences and the American College of Medical Informatics in 2001. Dr. Boguski is a graduate of the Medical Scientist Training Program at Washington University in St. Louis. His research background and interests are detailed at http://www.markboguski.net/themes.htm.

Wylie Burke, M.D., Ph.D., is professor and chair of the Department of Bioethics and Humanities at the University of Washington. She received a Ph.D. in genetics and an M.D. from the University of Washington and completed a residency in internal medicine at the University of Washington. She was a medical genetics fellow at the University of Washington from 1981 to 1982. Dr. Burke was a member of the Department of Medicine at the University of Washington from 1983 to 2000, where she served as associate director of the Internal Medicine Residency Program from 1988 to 1994 and as founding director of the University of Washington's Women's Health Care Center from 1994 to 1999. She was appointed chair of the Department of Medical History in October 2000. She is also an adjunct professor of medicine and epidemiology and an associate member of the Fred Hutchinson Cancer Research Center. She was a visiting scientist at the Centers for Disease Control and Prevention in 1998 and is a Fellow of the American College of Physicians. She has served on the NIH National Advisory Council for Human Genome Research and the Secretary's Advisory Committee on Genetic Testing. Dr. Burke's research addresses the social, ethical, and policy implications of genetic information, including genetic test evaluation, the development of practice standards for genetically based services, and genetics education for health professionals. She is also the director of the University of Washington Center for Genomics and Healthcare Equality, a center of excellence in ethical, legal, and social implications research funded by the National Human Genome Research Institute.

Roy Gandolfi, M.D., is an associate medical director at SelectHealth Insurance. SelectHealth is the insurance arm of Intermountain Health Care, a nonprofit company providing care to the intermountain West. His responsibilities include evaluating quality initiatives; adopting utilization guidelines, including genetic testing coverage; and pharmaceutical management. He participates in Intermountain's Clinical Genetics Institute. He is a practicing general internist and is an associate adjunct professor of medicine at the University of Utah. His undergraduate and medical degrees were obtained from the University of Michigan. Residency training was accomplished at the University of Utah.

Anna D. Garrett, Pharm.D., BCPS, is manager of outpatient clinical pharmacy programs for Mission Hospitals. Dr. Garrett received her bachelor and doctorate degrees in pharmacy from the University of North Carolina at Chapel Hill. She also holds a bachelor's degree in business administration with an accounting concentration from the University of North Carolina at Chapel Hill. Dr. Garrett completed a residency in hospital pharmacy practice at Wake Forest University Baptist Medical Center in 1991. She has practiced in the areas of infectious diseases and ambulatory care in both the hospital and physician office settings. Before coming to Mission she was the director of clinical pharmacy at Cornerstone Health Care in High Point, N.C. In her current position, she is responsible for managing existing pharmacist-run clinics and the expansion of pharmacist services in the outpatient environment. Dr. Garrett is also coordinating the activities of providers in the Asheville Project®, a nationally recognized program of patient self-management for chronic diseases. Dr. Garrett is also president and founder of the National Association of Women in Health Care, an organization that is dedicated to promoting the importance of self-care for women working in health care.

Karen Kaplan covers science for the *Los Angeles Times*. Since joining the desk in 2005, she has focused on genetics, stem cells, cloning, and the science of food and agriculture. Her coverage of genetics includes stories on the unreliability of DNA testing kits marketed directly to consumers over the Internet, the U.S. military's record of discriminating against service members with genetic disorders, the pros and cons of relying on DNA to decide who is a Native American, and the controversial theory that the reason debilitating genetic diseases persist among Ashkenazi Jews is that the mutations that cause them also boost intelligence. Before joining the science desk, Kaplan spent 10 years covering technology in the paper's business section as a reporter and editor. She studied economics and political science at MIT (where some of her friends decoded DNA by hand for the Human Genome Project in the early 1990s) and earned her master's degree in journalism from Columbia University in 1994.

Arthur N. Lurvey, M.D., F.A.C.P., FACE, is a board certified internist and endocrinologist and has been a Medicare contractor medical director for 14 years, initially working for the California Part B Carriers Transamerica Occidental Life Insurance Company, National Heritage Insurance Company, and National Government Services and, most recently, for Palmetto GBA, the Medicare contractor in jurisdiction J-1. He was in clinical practice for 35 years. Dr. Lurvey received his M.D. degree from the University of Illinois and had his postdoctoral and fellowship training at Los Angeles County-USC Medical Center. He is a delegate to both the California Medical Association

and the American Medical Association, has been a past hospital chief of staff, and serves on the quality and the CHART committees of the Hospital Council of Southern California. He also is on the board of the California Region of the American College of Physicians and on several committees of the American Association of Clinical Endocrinologists. Dr. Lurvey is a member of the American College of Physician Executives. Other medical activities include service as a CMA surveyor for both the Joint Commission hospital survey program and the continuing medical education accreditation program in California.

Donald O. Lyman, M.D., DTPH, currently serves as chief of the Division of Chronic Disease and Injury Control in the California Department of Health Services (CDHS). This division addresses prevention of the leading causes of death, illness, disability, and medical care costs. It houses the state's premier tobacco control program (realized a 40 percent reduction in smoking rates, a 65 percent reduction in tobacco consumption and a 26 percent decrease in tobacco-related cancer rates); a statewide cancer registry; control programs directed to cardiovascular diseases and diabetes; and a host of other categorical prevention programs. It is now working on public health's interface with the medical care industry to realize the potential benefits of prevention in the managed care setting. Dr. Lyman received his B.A. in chemistry from the University of Pennsylvania, his M.D. from Yale University, and his DTPH from the London School of Hygiene and Tropical Medicine. He did his residency training at the University of Miami (Florida) and UCSD. He has worked at the Centers for Disease Control and Prevention in various state, national, and international capacities. He has been the disease control officer (State Epidemiologist) for both New York and California and has been with the CDHS since 1978.

Elizabeth Mansfield, Ph.D., is the director of the personalized medicine staff in the Office of In Vitro Diagnostic Devices in the Center for Devices, FDA, where she is developing a program to address companion and novel diagnostic devices. She was previously a senior policy analyst in the Office of In Vitro Diagnostic Devices, managing policy and scientific issues. Dr. Mansfield formerly served as the director of regulatory affairs at Affymetrix, Inc. from 2004 to 2006. She has also served in other positions at FDA, including scientific reviewer and genetics expert. Dr. Mansfield received her Ph.D. from Johns Hopkins University and completed postdoctoral training at the National Cancer Institute (NCI) and the National Institute for Arthritis, Musculoskeletal, and Skin Diseases (NIAMS).

Dennis Salisbury, M.D., FAAFP, is an alumnus of Whitworth College and of the University of Washington School of Medicine, class of 1989. He finished

his transitional internship at Deaconness Medical Center (Spokane, Washington) in 1990, his residency in family medicine at Phoenix Baptist Medical Center (Phoenix, Arizona) in 1993 and a fellowship in interventional and high risk obstetrics at Family Medicine Spokane in 1994. Since then he has practiced full-time at the Rocky Mountain Clinic in Butte, Montana, a private multispecialty group. He is also an associate professor of healthcare informatics at Montana Tech University and the physician liaison for careQuest, an inpatient electronic medical record, at St. James Healthcare in Butte. He is secretary-treasurer of the Montana Academy of Family Physicians and a former president of that organization. He has served on the Commission for Continuing Professional Development of the American Academy of Family Physicians (AAFP) and was chair of its Subcommittee for Assembly Scientific Program; he has been an alternate delegate to the AAFP's Congress of Delegates twice. He serves on the EGAPP Stakeholders' Group and spoke at the inaugural GAPPNet meeting in Ann Arbor last October. As a product of his marriage, he has done personal practicum work in genetics three times, one of which involved the splitting of a zygote into two. (That is, he has three children, two of whom are identical twins.) He has speculated that the zygote splitting was caused by riding on a high-speed roller coaster, but he is reluctant to engage in further experiments to verify this hypothesis. His partner in this practicum would like it to be pointed out she did more of the work than he did. Other research includes participating in the Translating Research in Post-Partum Depression study through the AAFP Research Network.

Andrew Spiegel, J.D., B.S., B.A., is chief executive officer of the Colon Cancer Alliance. Mr. Spiegel, an attorney, was previously a founder and board member of the alliance. His goals are to bring national attention to this disease by promoting screening compliance, soliciting funds dedicated to this cancer, and helping to diminish the alarming number of unnecessary deaths from this very preventable disease. Spiegel has a long and personal history with colorectal cancer. In 1998, Spiegel's mother was diagnosed with metastatic colon cancer and died nine months later. It was then that Spiegel and a group of others founded the CCA to help bring greater public awareness to the disease and to provide support for those already affected. Since then, the CCA has grown tremendously and remains the leading advocacy group to battle colorectal cancer. Spiegel is a 1986 graduate of Temple University in Philadelphia, where he earned a Bachelor's degree in political science with minors in English and philosophy. He is a 1989 graduate of the Widener University School of Law where he was an editor of the *Delaware Law Forum*, an invited member of the Phi Delta Phi legal honors society, and a member of the Moot Court Honor Society. After working for a Philadelphia litigation firm, Spiegel opened his own law firm

in 1995 and is a participating member of numerous legal organizations in the region.

Vance Vanier, M.D., is the CEO and president of Navigenics. Dr. Vanier has spent the last decade of his career dedicated to prevention and personalized medicine. After working as an emergency physician on the front lines of medicine and seeing the overwhelming need for new preventive technologies, Dr. Vanier became a partner in the life sciences practice at Mohr Davidow Ventures (MDV). At MDV, Dr. Vanier invested in and helped build groundbreaking companies in the molecular and electrical diagnostic space, including iRhythm, CardioDx, and Crescendo Biosciences. Recognizing the early promise of preventive genomics, he joined Navigenics in 2008 as the company's chief medical officer. He created a vision for Navigenics built around a powerful idea—that the most effective and responsible way to introduce preventive genomic testing to the public was with the support and partnership of corporate medical directors, medical centers, and physician offices, in addition to Navigenics' own team of genetic counselors. Within 2 years, he built a series of clinical collaborations and distribution relationships that have made Navigenics the No. 1 physician-endorsed company in the preventive genomics space. These achievements include launching the Scripps Genomic Health Initiative, the largest behavioral genomics initiative in history; partnering with premier national physician groups such as MDVIP with its 100,000 covered lives; and building a network of large self-insured marquee employers who are incorporating Navigenics into their wellness and benefit programs. In further developing these and future partnerships, Dr. Vanier is committed to the belief that the transformative value of preventive genomics lies in its ability to motivate behavior change and medical compliance. Dr. Vanier continues to serve on the clinical faculty of Stanford Medical Center. Dr. Vanier received his medical degree from the Johns Hopkins School of Medicine and completed his residency training at the University of California, San Francisco, and Highland Hospital in Oakland, California. He received an M.B.A. from Stanford University as well as dual bachelor's degrees with honors.

David Veenstra, Pharm.D., Ph.D., is an associate professor in the Pharmaceutical Outcomes Research and Policy Program in the Department of Pharmacy, and a member of the Institute for Public Health Genetics at the University of Washington. Dr. Veenstra's methodological expertise is in cost-effectiveness modeling, including decision analysis, Markov modeling, and Monte Carlo simulation. Dr. Veenstra also has significant experience in developing disease simulation and cost-effectiveness models for chronic diseases, particularly hepatitis B. As part of an ongoing series of Academy of Managed Care Pharmacy educational programs, Dr. Veenstra has worked

extensively with formulary managers to assist them in evaluating cost-effectiveness models submitted to health care plans by manufacturers. He graduated from the University of California, San Francisco, with doctoral degrees in clinical pharmacy and computational chemistry. He conducted his postdoctoral training in outcomes research with the University of Washington, including a 1-year externship with Roche Global Pharmacoeconomics. Dr. Veenstra's primary research interests are the clinical, economic, and policy implications of pharmacogenomic-based drug therapies. His major research projects include association studies of genetic variants with the outcomes of warfarin treatment and cost-effectiveness studies of genetic tests for warfarin, breast cancer, and lung cancer therapies. Dr. Veenstra's other major research interest is the development of disease simulation models for chronic diseases, particularly hepatitis B. He has worked extensively with the Academy of Managed Care Pharmacy to develop guidelines and train decision makers in the practical application of cost-effectiveness models. Dr. Veenstra is an author on over 60 scientific articles, including publications in the journals *JAMA*, the *New England Journal of Medicine*, and *Science*. Dr. Veenstra is a member of the International Society for Pharmacoeconomics and Outcomes Research and of the International Health Economics Association. Dr. Veenstra is a past recipient of the PhRMA Foundation Career Development Award in Pharmacoeconomics.

Catherine A. Wicklund, M.S., CGC, is the director of the graduate program in genetic counseling at Northwestern University and an assistant professor in the Department of Obstetrics and Gynecology. She received her masters in genetic counseling from the University of Texas-Graduate School of Biomedical Sciences. She has 15 years experience in clinical genetic counseling and has provided prenatal and pediatric genetic services. Before she joined Northwestern, she co-directed the graduate program in genetic counseling at the University of Texas. While at the University of Texas she was also the director of genetic counseling services in the Department of Obstetrics, Gynecology, and Reproductive Medicine. She served on the board of directors of the National Society of Genetic Counselors, first as Region V representative, then as secretary, and was president in 2008. As a leader in NSGC she has represented the organization on several national committees, including the Secretary's Advisory Committee on Genetics, Health, and Society. She is also active on a state level and is working with the Illinois Department of Public Health on genetics education and finance and reimbursement issues, and she is on the Genetic and Metabolic Diseases Advisory Committee.

Janet Williams, M.A., CGC, is the coordinating genetic counselor for the Intermountain Healthcare Clinical Genetics Institute in Salt Lake City, Utah.

In addition to providing patient counseling, she has worked in program development in many clinical settings. Currently, she is actively involved in cancer genetics program development, the integration of family history information into the medical record, and development of reimbursement strategies for genetic counselors.

Marc S. Williams, M.D., FAAP, FACMG, is an alumnus of the University of Wisconsin-Madison, having graduated with a B.S. in Chemistry in 1977, and an M.D. in 1981. He did a pediatric residency at the University of Utah from 1981–1984. After 2 years of solo practice in Hillsdale, Michigan, he joined the Riverside (California) Medical Clinic as a general pediatrician and practiced there until 1991. From 1991 until joining Intermountain Healthcare, Dr. Williams was at the Gundersen Lutheran Medical Center in La Crosse, Wis. Hired as a general pediatrician, he eventually pursued fellowship training in clinical genetics and was board certified in this specialty in 1996 and recertified in 2006. In 1999 he gave up general pediatric practice and became the associate medical director of the Gundersen Lutheran Health Plan while maintaining his genetic practice. It was by combining these two areas of expertise that he developed an interest in the role of genetics in health care delivery. He has published and presented extensively on this topic. Since January 2005, he has been the director of the Intermountain Healthcare Clinical Genetics Institute in Salt Lake City, Utah. In addition to his administrative duties, Dr. Williams runs a clinic for evaluation of adults with mental retardation, birth defects, and genetic disorders. He is a clinical professor of pediatrics in the Division of Medical Genetics and adjunct professor of biomedical informatics at the University of Utah. He is a director of the board of the American College of Medical Genetics and in 2009 was elected vice president of clinical genetics. He has been a participant in the Personalized Medicine Workgroup of the Department of Health and Human Services' American Health Information Community Task Force, vice chair of the EGAPP Stakeholder's Group at the Centers for Disease Control and Prevention, a member of the CDC's CETT program review board, and a member of the Secretary's Advisory Committee for Genetics, Health and Society, having previously served on the Coverage and Reimbursement Task Force of that group. He is past chair of the Committee on the Economics of Genetic Services of the American College of Medical Genetics as well as chair of the subcommittee on Health Care Systems of the Section on Genetics and Birth Defects of the American Academy of Pediatrics. He chairs the American College of Medical Genetics Quality Improvement Special Interest Group. He is the editor-in-chief of the *Manual on Reimbursement for Medical Genetic Services*. He has authored more than 40 articles in the peer-review medical literature and has presented more than 50 papers at national and international meetings.

David R. Witt, M.D., is a medical geneticist at Kaiser Permanente in San Jose, California. His clinical practice includes a broad spectrum of general medical genetics, including dysmorphology, teratology, prenatal diagnosis, and inherited diseases of children and adults. He is the director of the Kaiser Permanente Regional Huntington Disease Predictive Testing Program. He is widely recognized for his work on population screening for cystic fibrosis and is the director of the Kaiser Permanente Prenatal Ethnicity-Based Screening Program. He has lectured on the role of medical genetics services in managed care and is the author of numerous research publications. Dr. Witt is board certified in medical genetics and pediatrics. He is a Fellow of the American College of Medical Genetics. He received his undergraduate degree from Brandeis University and his medical degree from Tufts University. His pediatric training was at the Massachusetts General Hospital, and his medical genetics fellowship was at the University of British Columbia.

Steven H. Woolf, M.D., M.P.H., is a professor in the departments of family medicine, epidemiology, and community health at Virginia Commonwealth University. He received his M.D. in 1984 from Emory University and underwent residency training in family medicine at Virginia Commonwealth University. Dr. Woolf is also a clinical epidemiologist and underwent training in preventive medicine and public health at Johns Hopkins University, where he received his M.P.H. in 1987. He is board certified in family medicine and in preventive medicine and public health. Dr. Woolf has published more than 100 articles in a career that has focused on evidence-based medicine and the development of evidence-based clinical practice guidelines, with a special focus on preventive medicine, cancer screening, quality improvement, and social justice. From 1987 to 2002 he served as science advisor to, and then member of, the U.S. Preventive Services Task Force. Dr. Woolf edited the first two editions of the *Guide to Clinical Preventive Services* and is author of *Health Promotion and Disease Prevention in Clinical Practice*. He is associate editor of the *American Journal of Preventive Medicine* and served as North American editor of the *British Medical Journal*. He has consulted widely on various matters of health policy with government agencies and professional organizations in the United States and Europe, and in 2001 he was elected to the Institute of Medicine.

Appendix C

Lynch Syndrome Topic Brief

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CLINICAL SCENARIO

Tumor screening and genetic testing for Lynch syndrome, i.e., mismatch repair (MMR) gene mutations (changes), in individuals newly diagnosed with colorectal cancer in order to identify patients with Lynch syndrome and to reduce morbidity and mortality from Lynch syndrome in relatives (EGAPP, 2009; Palomaki et al., 2009).

PUBLIC HEALTH IMPORTANCE

Individuals with Lynch syndrome, sometimes referred to as hereditary non-polyposis colorectal cancer (HNPCC), have a high risk of developing colorectal cancer as well as other cancers, particularly endometrial. The increased risk is due to mutations in mismatch repair genes which reduce the ability of cells to repair DNA damage. Approximately 20 to 65 percent of individuals with Lynch syndrome develop colorectal cancer during their lifetimes, whereas lifetime risk in the general population is approximately 5.0 percent. Of the approximately 142,000 new cases of colorectal cancer diagnosed each year, approximately 4,250 (about 3 percent of all patients) are attributable to Lynch syndrome. In addition, about half of the close biological relatives of those colorectal cancer patients with Lynch syndrome, about 8,000 relatives, also have Lynch syndrome and are at high risk. Screening for colorectal cancer substantially reduces the risk of developing colorectal cancer and is recommended for the general population beginning at age 50. Annual or biennial screening colonoscopy at an early age in

individuals at high risk of Lynch has been found to reduce risk of colorectal cancer by about 60 percent. Genetic testing for MMR gene mutations can identify individuals with Lynch syndrome. Identifying Lynch syndrome in newly diagnosed colorectal patients and offering testing to relatives of patients with Lynch could identify relatives with Lynch syndrome before they develop cancer and allow them to reduce their risk through screening. Potentially, more than 2,500 cases of colorectal cancer could be prevented each year if all individuals with Lynch were identified and screened early (Baglietto et al., 2009; EGAPP, 2009; Horner et al., 2009; Palomaki et al., 2009; Stoffel et al., 2009; U.S. Cancer, 2009; U.S. Preventive Services Task Force, 2008).

Test Purpose

Screening: a test to identify patients with colorectal cancer who should be offered confirmatory molecular testing.

Diagnostic: a test to confirm that the person has a specific genetic condition.

Test Description

DNA analysis of 4 major MMR genes (*MLH1, MSH2, MSH6,* and *PMS2*) is the standard test for Lynch (Bonis et al., 2007; EGAPP, 2009; Palomaki et al., 2009). Because of the cost of MMR testing, 3 preliminary tests on tumors may be considered in patients with colorectal cancer in order to determine whom to test for MMR mutations. Microsatellite instability (MSI) testing identifies tumors demonstrating abnormalities of DNA mismatch repair. Patients with a high instability score can be offered DNA sequencing of the 4 MMR genes. Immunohistochemical (IHC) staining tests of tumors identify proteins produced by MMR genes. Patients with no staining of a specific protein can be offered DNA analysis of the MMR gene identified by IHC. About 30 percent of tumors that lack staining for the MLH1 protein have a somatic mutation in *BRAF* (V600E) or *MLH1* promoter hypermethylation, neither of which is associated with Lynch syndrome. *BRAF* gene testing and *MLH1* promoter hypermethylation may be done for patients who have no IHC staining for MLH1. Patients who do not have the *BRAF* mutation or *MLH1* promoter hypermethylation can be offered DNA analysis of *MLH1*. *MLH1* promoter hypermethylation was not considered in the published evidence reviews. Other test combinations are sometimes used (Bonis et al., 2007; EGAPP, 2009; Palomaki et al., 2009).

Systematic Evidence Reviews

Agency for Healthcare Research and Quality, Evidence Report/Technology Assessment (Bonis et al., 2007).

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Supplemental Evidence Review (Palomaki et al., 2009).

Recommendations by an Independent Group[1]

The EGAPP Working Group recommended offering genetic testing for Lynch syndrome in individuals newly diagnosed with colorectal cancer in order to reduce morbidity and mortality in relatives (EGAPP, 2009).

Guidelines by Professional Groups

American Society of Clinical Oncology (Locker et al., 2006).

National Comprehensive Cancer Network (National Cancer Center, 2010).

EVIDENCE OVERVIEW

Analytic Validity

The accuracy and reliability of the tests in detecting the genetic changes of interest.

Based on evidence reviews, the EGAPP Working Group reported that, overall, the analytic validity of the tests is high, although there were gaps in research on analytic validity and proficiency testing, as described below (Bonis et al., 2007; EGAPP, 2009; Palomaki et al., 2009).

MMR: DNA sequencing of 4 MMR genes (*MLH1, MSH2, MSH6,* and *PMS2*) is the practice standard, but actual performance is difficult to estimate and it is not known if laboratory proficiency testing will be an adequate validity measure. In addition, research may identify additional MMR genes (Yu et al., 2010).

MSI: Testing is offered by many laboratories that participate in proficiency testing programs, and performance in such testing programs is high, so adherence to best practices may provide valid testing.

[1] Independent groups include the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, the Evaluation of Genomic Applications in Practice and Prevention (EGAPPP) Working Group, the United Kingdom's National Institute for Health and Clinical Excellence, and the U.S. Preventive Services Task Force (USPSTF).

IHC: IHC proficiency testing is offered for other proteins but not specifically for MMR gene proteins.

BRAF: Given that the goal of this test is to identify a single mutation and that proficiency testing for some other single-mutation tests has been high, analytic validity is likely to be high.

Clinical Validity

The accuracy and reliability of the test in identifying patients with the disorder.

Based on the evidence reviews, the EGAPP Working Group reported that there is adequate evidence of clinical validity for the preliminary tests, although the evidence varied and research gaps were identified for the issues of which tests and which combinations perform best and the use of family history with tests, as described below (Baglietto et al., 2009; Bonis et al., 2007; EGAPP, 2009; Palomaki et al., 2009; Stoffel et al., 2009).

MMR: DNA sequencing of 4 MMR genes (*MLH1, MSH2, MSH6,* and *PMS2*) is the current standard for defining patients with Lynch syndrome. The lifetime risk of colorectal cancer among individuals with Lynch syndrome is approximately 20 to 65 percent.

MSI: Studies enrolling a total of 150 patients with Lynch syndrome and using a variety of MSI methods found that high MSI score test results are adequately sensitive and specific in identifying individuals who had tested positive for some MMR genes.

IHC: Studies with a total of 149 patients found that IHC testing is adequately sensitive and specific in identifying individuals who test positive for some MMR genes.

BRAF: A few studies found *BRAF* mutation tests are adequately sensitive and specific in identifying individuals with abnormal MLH1 staining.

Clinical Utility

The possibility that using the test will lead to improved health.

Based on the evidence reviews, the EGAPP Working Group reported that there is adequate evidence from research that more than 90 percent of relatives of patients with Lynch would consent to genetic testing and that more than half of those who were identified as having Lynch syndrome began screening with colonoscopy, beginning at age 20–25. A single study

of relatives at high risk provides evidence that screening colonoscopy results in an approximately 60 percent reduction in the incidence of colorectal cancer. Harms appear to be minimal in comparison with benefits. However, additional research is needed on the overall strategy, or each step from offering genetic testing to patients through studying the long-term health benefits to relatives. Additional cost–benefit analyses are also needed (Bonis et al., 2007; EGAPP, 2009; Palomaki et al., 2009). Screening or prophylactic surgery for prevention of other Lynch-syndrome-associated cancers (particularly endometrial) have not been assessed for utility. A cost-effectiveness analysis has reported an incremental cost-effectiveness ratio of less than $45,000 per quality-adjusted life-year saved for a Lynch syndrome testing strategy using tumor screening and genetic testing for all individuals newly diagnosed with colorectal cancer (Mvundura et al., 2010).

Contextual Issues

Including clinical alternatives to genetic testing and practice; ethical, legal, and social issues.

The EGAPP Working Group found that, based on the evidence reviews, methods using family history to identify patients with Lynch produce inconsistent results and identify a lower percentage of patients with Lynch than do tumor-based screening protocols. However, MMR testing of patients based on family history was not excluded. The working group also recommended informed consent for preliminary testing of patients and noted that studies suggest adverse psychosocial outcomes should be minimal and that resource requirements appear to be justified by the willingness of relatives to participate in health benefits for relatives (Bonis et al., 2007; EGAPP, 2009; Palomaki et al., 2009). A recent report suggests that more research is needed on psychosocial issues because of evidence that some subgroups are more vulnerable to testing-related stress (Landsbergen et al., 2009). Overall, there is limited research on how to effectively implement testing.

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Appendix D

Warfarin Topic Brief

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CLINICAL SCENARIO

Warfarin is a commonly used anticoagulant that is prescribed for the prevention of thromboembolic events in patients with such indications as atrial fibrillation, previous thromboembolism, and artificial heart valves. Warfarin has a narrow therapeutic index: Too high a dose can lead to major bleeding and too low a dose does not protect from thromboembolic events. In addition, there is high variability in response to the drug both between patients and for a single patient at different points in time. Warfarin therapy is thus carefully managed, with the International Normalized Ratio (INR) used to monitor anticoagulation response and monitoring and dose adjustment occurring every 2–6 weeks. The use of genomic information may improve the ability to predict an optimal initial dose, thus improving therapeutic response during warfarin initiation, when the risk of over-anticoagulation and major bleeding events is highest.

PUBLIC HEALTH IMPORTANCE

Warfarin-related bleeding is one of the most common causes of serious adverse drug events leading to hospitalization.

Test Purpose

Predictive: drug treatment response and safety.

Systematic Evidence Reviews

An evidence-based review conducted in 2006 by the American College of Medical Genetics (Flockhart et al., 2008) found that *CYP2C9* and *VKORC1* testing to guide warfarin dosing had analytic and clinical validity. However, the review found that "no study has yet shown this intervention to be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events." A recent systematic review by Kangelaris and colleagues also reported a lack of evidence of benefit (Kangelaris et al., 2009).

Regulatory Guidance

On January 22, 2010, the FDA modified the drug label for warfarin to include dose ranges based on pharmacogenomic information. This was an update to the 2007 label change that had added information about the association between *CYP2C9* and *VKORC1* variants and warfarin responsiveness. Both label changes inform the prescriber about the association between genotype and warfarin dosing requirements, but they do not require pharmacogenetic testing.

Guidelines by Professional Groups

The 2008 American College of Chest Physicians anticoagulation management guidelines state, "[W]e suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C)" (Ansell et al., 2008).

Recommendations by Payers

CMS recently issued a coverage decision for warfarin pharmacogenomic testing that specifies testing will be reimbursed only for patients initiating warfarin who are enrolled in a randomized controlled trial that measures major bleeding and thromboembolic events.

EVIDENCE OVERVIEW

Analytic Validity

Testing for the two to three informative *CYP2C9* SNPs and the single informative *VKORC1* SNP is straightforward.

Clinical Validity

Together, the *CYP2C9* and *VKORC1* variants account for approximately 30 percent of the variance in warfarin dose requirement, while clinical and demographic factors account for approximately 20 percent of the variability (Limdi and Veenstra, 2008). A warfarin dose prediction algorithm was recently developed by the International Warfarin Pharmacogenetics Consortium (IWPC) using data from 5,700 patients from 9 countries (Klein et al., 2009). Dose prediction that included pharmacogenetic information improved the ability to accurately predict those patients who required ≤ 3 mg/day (54.3 percent versus 33.4 percent) and those who required ≥ 7 mg/day (26.4 percent versus 9.1 percent) compared to using clinical and demographic information only. The risk of major hemorrhage in patients with a variant of *CYP2C9* is approximately double that in *CYP2C9* wild-type patients (Higashi et al., 2002; Limdi et al., 2008). In contrast, *VKORC1* appears to confer a higher risk of over-anticoagulation (INR > 4) (Meckley et al., 2008; Schwarz et al., 2008) during the first few days of therapy, but not a bleeding risk (Limdi et al., 2008).

Clinical Utility

The impact of genotype-guided dosing on clinical outcomes has been compared with standard care in two small randomized controlled trials, but the results were not definitive. Caraco et al. reported a shorter time to first therapeutic INR and first stable INR among patients receiving *CYP2C9* (only) genotype-guided therapy (Caraco et al., 2008). A more recent, higher-quality study by Anderson et al. in 200 patients found no difference in the percentage of INRs within therapeutic range (Anderson et al., 2007), although the effect of genotyping may have been mitigated because 80 percent of the subjects were inpatients and closely monitored. An NIH-funded randomized controlled trial—the Clarification of Optimal Anticoagulation Through Genetics (COAG) trial—has recently been initiated to study this issue further (Clinicaltrials.gov, 2008). The trial will enroll approximately 1,200 patients, measure the percentage of time in therapeutic range over the first month as the primary outcome, and compare clinical versus clinical plus genomic algorithms for dose initiation. The trial is scheduled for completion in the fall of 2011.

Cost Effectiveness

An early (non-peer reviewed) cost-effectiveness analysis suggested that warfarin pharmacogenomic testing, if implemented throughout the

United States, could save $1 billion annually (McWilliam et al., 2006). However, the assumptions in this study have been criticized (Hughes and Pirmohamed, 2007; Veenstra, 2007). Several more recent studies have come to the conclusion that warfarin pharmacogenomic testing is unlikely to be cost effective unless testing costs drop significantly and the uncertainty around effectiveness is reduced (Eckman et al., 2009; Meckley et al., 2010; Patrick et al., 2009).

Summary

Variation in the *CYP2C9* and *VKORC1* genes clearly affects warfarin dosing requirements, but given that anticoagulation status is (or should be) already closely monitored and individualized in warfarin patients, the incremental benefits of pharmacogenomic testing are less clear (Eckman et al., 2009; Schwarz et al., 2008). The convincing evidence of clinical validity, the unclear evidence of clinical utility, and the contrasting perspectives of stakeholders on the value of warfarin pharmacogenomic testing make it an interesting case study.

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Appendix E

Genomic Profiling Topic Brief

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ANNE'S STORY

Anne is a recently divorced 36-year-old MBA financial analyst. She has always considered herself to be both healthy and health conscious. She is an only child, with a mother of English ancestry and a father of mixed Eastern European descent. Her past medical history is notable only for a mildly abnormal glucose tolerance test at age 31 during her second pregnancy. This was not medically followed subsequent to the pregnancy. Anne prides herself on her careful diet, and she runs on a treadmill at a workplace gym at least 3 times a week. Despite these efforts she is 15 pounds overweight according to a table that she found in a popular magazine. She has never smoked. She has been tired lately, perhaps related to the demands of single motherhood.

Anne's mother is 67 years old and was treated at age 59 for melanoma, but Anne knows no further details. Her mother has recently had mildly elevated blood sugars, and her doctor is considering beginning oral hypoglycemic therapy. Anne's father is 70 and is taking a statin for hypercholesterolemia and a beta-blocker for hypertension. He had a very mild heart attack in his late 40s and takes prophylactic aspirin. Two of the father's maternal first cousins are said to have died of colon cancer in their 40s, but, again, no details are available. His paternal aunt died of breast cancer in her late 30s. There may be other relevant conditions in the family history, but no physician has ever asked Anne about them.

Anne has read articles in the *New York Times* and elsewhere about the availability of genomic screening for health risk assessment. As is her usual

practice in health-related matters, Anne extensively reviewed the topic on the Internet and compared the tests offered by several different companies. She is especially concerned about her future risk of diabetes and coronary artery disease, based on her personal and family histories, so she selects the lab that places the greatest emphasis on these conditions on its website.

When Anne returns from vacation, a printed report awaits her. If she understands the report correctly, she is relieved to learn that her risk of type 2 diabetes is 10 percent below that of the general population. On the other hand, her future risk of coronary artery disease is 20 percent above the general population risk. It is unclear from the report if the risks have taken her family or personal histories into account or if the risks were calculated exclusively based on the genomic results. As she continues to read the report, Anne learns that her breast cancer risk is 30 percent above the general population risk and she is dismayed to read that her Alzheimer's disease risk is double that of the general population. Finally, she is surprised and confused when she reads that she is a carrier for hemochromatosis and alpha-1 antitrypsinase deficiency, two conditions with which she is entirely unfamiliar. She wonders if these findings might explain her recent fatigue.

Anne immediately calls her doctor's office, but the earliest available appointment is not for two weeks. When she arrives for the appointment she appears to be mildly agitated. She brings a copy of the report and has a two-page list of hand-written questions prepared for her doctor. Here are the questions on the first page:

What is hemochromatosis and alpha-1 antitrypsinase deficiency? Does this explain my fatigue? What other symptoms should I expect? How could I possibly have two rare conditions that I never even heard of before? Does a lab like this ever make mistakes? Do you think I should send a sample to another lab for confirmation of my results?

I remember my obstetrician telling me that my abnormal blood sugar test during pregnancy might increase my later risk for the development of diabetes and now my mother seems to be developing late-onset diabetes. How reassured should I be by the report that says I am at lower risk than the general population for diabetes? I have been watching my sugar intake. Can I relax my diet now?

With my father's history of an early heart attack I always assumed I might be at increased risk and my test result confirms my suspicions. What should I do about this?

I'm really worried about breast cancer. With a 30 percent increased risk, should I start receiving mammograms earlier than age 40?

I'm really scared by my increased risk for Alzheimer's disease. Is there anything I can do to reduce my risk?

I have a family history of early onset colon cancer, although it's only in my cousins. I was disappointed that my report didn't say anything about my colon cancer risk. Do you think I should send a sample to another company that will test for colon cancer risk?

Now I'm worried about my children. I would like to have them tested as soon as possible. What do you think about that idea?

I am hoping to convince my insurance company to pay for my test. When I spoke to the company representatives they said something about "medical necessity," but I didn't understand it fully. Can you write a letter of support?

The questions on Anne's second page are more difficult to answer and are left to the imagination of the discussants.

BASIC CONCEPTS AND DEFINITIONS IN GENETICS

Association

The joint occurrence of two genetically determined characteristics in a population at a frequency that is greater than expected according to the product of their independent frequencies.

In simpler terms, any two events that occur together at a non-random frequency are associated. The relationship is statistical and does not imply (nor does it exclude) causality. The concept of association predates the elucidation of the human genome and, with respect to common diseases, is meaningful not only at the DNA level but also at the level of protein variations and at the level of observable physical characteristics. As an example of a protein-level association, it has been known for many decades that peptic ulcer disease is non-randomly associated with blood type, with individuals of blood type A and O being at higher lifetime risk for this illness than individuals of other blood types. As an example of an association at the level of observable physical characteristics, it is well established that the incidence of prostate cancer varies by ethnic/racial group, with Asians at low risk and African Americans at particularly high risk. Given the fact that protein and physical variations have a basis in variations at the DNA level, it is not surprising that the principles of association extend to the genomic level.

Single Nucleotide Polymorphism (SNP)

A DNA sequence variation occurring when a single nucleotide in the genome differs between individuals (or between paired chromosomes in a single individual).

For example, if the sequences for the same DNA fragments from different individuals are AAGC**C**TA and AAGC**T**TA, we can see that the fragments are different in a single nucleotide. For such a variation to be considered a SNP, it must occur in at least 1 percent of the population. SNPs are extremely common, making up about 90 percent of all human genetic variation and occurring every 100 to 300 bases along the 3 billion base human genome. Most SNPs are "silent" and have absolutely no effect on protein structure or observable physical characteristics. The description of the human genome has provided a greatly magnified view of human genetic variation and offered a widely expanded opportunity to look for associations of these genomic variants with common diseases. Another common way of describing such associations is to speak of a SNP as a "marker" for predisposition to an associated disease.

Genome-Wide Association Study (GWAS)

An examination of genetic variation across the entire genome, designed to identify associations of DNA variants with observable traits.

The primary goal of most GWAS studies is the identification of disease associations that will provide biological insights into disease pathogenesis. The application of GWAS findings to personalized risk assessment may be viewed as a clinical byproduct of epidemiologically motivated research. Because of the large number of relatively weak associations that may be identified in a GWAS study, it is inevitable that some statistically significant associations will be spurious. As a general rule, associations are therefore deemed relevant only after replication in multiple GWAS studies.

To illustrate, a GWAS study of bipolar disease would require two populations, one composed of patients with bipolar disease and the other a control population consisting of people without known bipolar disease. The genomes of both groups would be analyzed, paying particular attention to SNPs (and other types of known genetic variation). Using the SNP described above, it might be found that the AAGC**C**TA variant was found in 4 percent of bipolar patients, with 96 percent of this group manifesting the more common AAGC**T**TA. If the control population revealed that only 3 percent possessed AAGC**C**TA, and if the sample size were large enough, the difference between 3 percent and 4 percent might be statistically significant, identifying an association between the "C" allele and bipolar disease.

It is important to point out that a "risk" allele such as "C" in this

example may confer only a small increase in the risk of the disease under study. In our example, most patients with "C" do not develop bipolar disease. It is, after all, seen in 3 percent of the healthy control population. Most patients with bipolar disease (96 percent) do not even have the "C" allele. Nevertheless, the data demonstrate that an individual with the "C" allele has a statistically higher chance of having bipolar disease than does an individual with the "T" allele. Since most genes are found in a single pair, the data might be further analyzed to show that individuals with "CC" genotypes are at higher risk of bipolar disease than are "CT" individuals, who are at higher risk than "TT" individuals.

The population prevalence of bipolar disease is approximately 1 percent. Inventing some results to continue our example, we might find that "TT" individuals have 0.9 percent risk, "CT" individuals have a 1.2 percent risk, and "CC" individuals have a 2 percent risk of bipolar disease. Care must be exercised when, in this example, the claim is accurately made that the "C" allele confers a 20 percent increased risk of bipolar disease because this effect, when expressed in this fashion, could exaggerate the practical importance of an increase from the population risk of 1 percent to a modified risk of 1.2 percent. While this example was entirely fabricated, the magnitude of risk adjustment allowed by GWAS-based associations is most commonly in a range similar to the example.

In real life, the issue is even more complicated, because a number of SNPs at different sites may be found to be associated with an increased or decreased risk of bipolar disease. The final calculation of risk requires a complex computational model that incorporates data from each of the SNPs selected for analysis. There is no universal consensus on SNP selection, so it is entirely possible for one model, using one set of SNPs, to predict an increased risk of bipolar disease, while another model, employing a different (perhaps overlapping) set of SNPs, predicts a different risk for the same individual. In the worst case scenario, one model could predict an increased risk whereas a second model could predict a decreased risk for the same individual.

Screening

The identification, among apparently healthy individuals, of those who are sufficiently at risk of a specific disorder to justify a subsequent diagnostic test or procedure or to direct preventive action.

The general requirements for a valid and clinically useful screening program are well established:

1. The disease must be well-defined.
2. The prevalence of the disease must be known.

3. The disease must be medically important.
4. There must be an effective treatment or preventive measure available.
5. The test must be simple, safe, widely available, affordable, and reliable.
6. The test should have an acceptably low risk of ambiguous results.
7. The test must be accompanied by adequate pretest counseling, informed consent, and follow-up services.

The World Health Organization has set forth a similar set of criteria[1]:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on who to treat as patients.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a "once and for all" project.

The Institute of Medicine has also offered a set of criteria[2]:

1. Genetic screening, when carried out under controlled conditions, is an appropriate form of medical care when the following criteria are met:

    a. There is evidence of substantial public benefit and acceptance, including acceptance by medical practitioners.
    b. Its feasibility has been investigated and it has been found that benefits outweigh costs; appropriate public education can be

[1] Wilson, J. M. G., and G. Jungner. 1968. Principles and Practice of Screening for Disease. *World Health Organization Public Health Papers No. 34*. http://whqlibdoc.who.int/php/WHO_PHP_34.pdf (accessed November 28, 2008).

[2] National Research Council, Committee for the Study of Inborn Errors of Metabolism. 1975. *Genetic Screening: Programs, Principles, and Research*. Washington, DC: National Academy of Sciences.

carried out; test methods are satisfactory; laboratory facilities are available; and resources exist to deal with counseling, follow-up, and other consequences of testing.

c. An investigative pretest of the program has shown that costs are acceptable; education is effective; informed consent is feasible; aims of the program with regard to the size of the sample to be screened, the age of the screenees, and the setting in which the testing is to be done have been defined; laboratory facilities have been shown to fulfill requirements for quality control; techniques for communicating results are workable; qualified and effective counselors are available in sufficient number; and adequate provision for effective services has been made.
d. The means are available to evaluate the effectiveness and success of each step in the process.

A number of commercial laboratories directly offer consumers an analysis of a large panel of selected SNPs that are used to calculate the future risk of developing a number of diseases in the tested individual. Surveying the websites of the three most prominent firms, Navigenics, 23andMe, and deCODE, there are 10 common diseases included in the panels of all three companies:

1. age-related macular degeneration
2. atrial fibrillation
3. breast cancer
4. celiac disease
5. Crohn's disease
6. prostate cancer
7. psoriasis
8. rheumatoid arthritis
9. type 2 diabetes mellitus
10. deep vein thrombosis

There are a number of additional conditions that appear on the list of one or two of these three companies. Examples include Parkinson's disease, Alzheimer's disease, lupus, osteoarthritis, multiple sclerosis, lung cancer, kidney stones, gallstones, and gout. Since testing is offered directly to consumers, a health professional typically has not been involved in the ordering of such tests or in pre-test counseling. The companies do have genetic counselors and other professionals on staff to address consumers' questions that may arise. Since most governmental bodies require that medical tests be performed only at the request of a physician or other qualified health

practitioner, these commercial firms emphasize that the service they offer does not constitute a medical test, as defined in the law. In an open letter to the medical community, 23andMe thus describes its service as follows:

> "Our service combines genotyping with a set of tools and features that depict each customer's personal information clearly, yet without distorting or misrepresenting our current understanding of how genes combine with environment and other factors to produce human traits and diseases. We also keep our service up-to-date by evaluating major genetic association studies as they are published in peer-reviewed journals, and incorporating them into our service after they have been satisfactorily confirmed.
>
> What we do not and will not do is provide medical advice to our customers. Though our service delivers personalized data, the information it provides is tailored to genotypes, not to individuals. Initially, we will have no knowledge of our customers' vital signs, disease histories, family histories, environment, or any other medically relevant information. Thus we have no way of evaluating our customers' health or medical needs, and we make every effort to clarify this for our customers.
>
> We also try to impress upon our customers the fact that genes are far from the only determinant of health, and that other factors can play an equal or greater role in determining whether they will develop a particular disease or condition. And our materials explain that the scientific understanding of how genetics may affect disease risk and other aspects of a person's health is changing and will continue to change as more research is done.
>
> These caveats aside, we at 23andMe believe that giving personalized genetic information to our customers can inspire them to take more responsibility for their own health and well-being. We also think our tools will serve to educate the lay public about genetics. At the very least, we hope our product will stimulate conversation among doctors, patients and researchers about genes and their role in human health."

Genomic analysis for the prediction of common disease risk has been a controversial practice. Proponents argue that individual autonomy requires unrestricted access to any potentially available genetic information. Efforts to limit access have been branded as paternalistic. This argument continues with the assertion that the discovery of reduced risk could be reassuring and the discovery of increased risk could motivate healthy changes in lifestyle that might mitigate the increased risk. For example, an individual found to be at a risk for type 2 diabetes that is higher than that of the general population might be spurred to institute a weight-reduction diet.

Opposing arguments point to the lack of consensus on the genetic markers selected for study and the consequent inconsistency of risk prediction. Risk modification is most typically of small magnitude (as in the example above) and often does not exceed the risk stratification that

could be achieved by more traditional methods (e.g., an assessment of weight and family history in predicting the risk of type 2 diabetes). Some of the conditions being assessed offer no clear risk-modifying intervention (e.g., rheumatoid arthritis) and some risk-modifying interventions are strongly indicated independent of one's genetic risk (e.g., smoking cessation is always recommended regardless of an individual's precise risk of lung cancer). Fears have been expressed that knowledge of reduced risk might encourage unhealthy lifestyle choices (i.e., a real risk of testing). Furthermore the paucity of pre-test counseling and the large panel of assessed risks raise concerns that patients will be unprepared to deal with the results. A patient motivated to seek testing because of a strong family history of prostate cancer may or may not be prepared to learn of his increased risk for the future development of Alzheimer's disease. Patients' personal physicians may not be in the best position to assist with result interpretation, as they had no role in ordering the tests and are unlikely to have received the requisite education to contribute any real expertise.

The majority of observers probably occupy some middle ground between these opposing opinions. This middle group points to the lack of evidence upon which to judge the clinical utility, safety, or cost-effectiveness of genomic risk assessment. There are many examples from the pre-genomic era of the failure to translate statistically validated risk stratification into an effective screening regimen or intervention. (Prostate cancer screening in African American men is a familiar example.) Neutral observers question the adherence of genomic risk assessment to the previously described principles of population screening. The current state of direct-to-consumer testing also runs the risk of exacerbating health disparities by offering an expensive test that is unlikely to be covered by health insurance (because of the lack of evidence of clinical utility or cost effectiveness). For example, the Navigenics website offers testimonials from its customers in a section titled "Success Stories." The selected group consists of an Internet entrepreneur, a psychotherapist, a software analyst, a venture capital executive, a journalist, an Internet executive, an attorney, a marketing consultant, and a marketing executive. Even by Silicon Valley standards, the tested group is highly unrepresentative of the general population. Such unequal access to service leads even those who recognize the potential health benefits of genomic risk assessment to wonder if it is possible to reconcile personalized medicine with public health.

ADDITIONAL READING

A number of professional societies have published policy statements regarding direct-to-consumer genomic testing. Depending on the focus of these societies, the statements either broadly or more narrowly address the

technical, clinical, ethical, legal and/or social aspects of such testing. These policy statements include:

The American College of Clinical Pharmacology:
Ameer, B., and N. Krivoy. 2009. Direct-to-consumer/patient advertising of genetic testing: A position statement of the American College of Clinical Pharmacology. *J Clin Pharmacol* 49:886–888.

The American College of Medical Genetics:
www.acmg.net/AM/Template.cfm?Section=Terms_and_Conditions&termsreturnurl=Section=Policy_Statements&Template=/CM/ContentDisplay.cfm&ContentID=2975, published 2008.

The American Society of Human Genetics:
Hudson K., G. Javitt, W. Burke, and P. Byers, with the ASHG Social Issues Committee. 2007. ASHG Statement on Direct-to-Consumer Genetic Testing in the United States. *Am J Hum Genet* 81:635–637.

The American Society of Clinical Oncology:
http://jco.ascopubs.org/cgi/reprint/JCO.2009.27.0660v1

The National Society of Genetic Counselors:
www.nsgc.org/about/position.cfm#DTC, adopted 2007.

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