

Virtual Mentor
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FROM THE EDITOR

Getting Personal: The Promises and Potential Pitfalls of Personalized Medicine

The potential of personalized medicine, a technology and method of medical reasoning that hinges closely upon an individual's genetic make-up, is just starting to be explored. About a decade has gone by since the complete sequencing of human DNA in the Human Genome Project, which promised new understanding of disease and new cures. Since then, further discoveries have revolutionized the medical sciences, and we are already starting to see the technology catch up to the promise. Advancements in disease and genome detection technologies, as well as the development of tailored therapies based upon genetic make-up, are appearing in research studies, early clinical trials, and even, in some cases, in clinical practice. With new technologies and new knowledge come unique challenges and ethical dilemmas. We can know more about an individual than we ever have before, and we must be certain that we are good stewards of this information, as clinicians, as patients, as policy makers, and as world citizens.

In our first case discussion, Rachel A. Mills, MS, Susanne B. Haga, PhD, and Geoffrey S. Ginsburg, MD, PhD, a founding director of the Institute for Genome Sciences & Policy at Duke University, explore a variation on a common ethical theme: namely, how much information a patient is entitled to accept or ignore about his or her health, particularly when the patient has dependents to consider and when personalized medical technology makes it possible to detect a health problem before it becomes symptomatic. The concepts of autonomy and beneficence come to the fore when personalized medicine offers clinicians the ability to predict disease and help patients and their families plan accordingly.

Our second case highlights a real-life dilemma encountered by several undergraduate programs and medical schools attempting to educate their students about personalized medicine. In these instances, schools are offering genetic testing for the students to give them a personal experience as a platform for discussing not only the technology but also its implications and counseling demands. Dr. John Mahoney, MD, addresses questions of coercion, privacy, and the responsibilities that come with using students' genomes for education purposes. Although this activity serves as an interesting and informative exercise, it is essential to ask whether the benefits outweigh the potential risks.

The final case, addressed by Jeffrey R. Botkin, MD, MPH, tackles a rising trend at research and academic hospitals regarding the collection and biobanking of tissue and blood samples for genetic research purposes. Personalized medicine benefits greatly from the creation of biobanks that store a wide array of genetic material for

researchers to sequence and correlate to disease activity. These correlations can then be used in attempts to generate potential treatments for the associated diseases. Some hospitals have elected to use leftover tissue samples and blood draws from their hospitalized patients, automatically enrolling them in biobanks rather than obtaining consent for enrollment by the traditional method. This “opt-out” strategy works well for gathering a large data set, but not without ethical controversy.

The contribution to *Virtual Mentor*'s medical education section takes its cue from the ethical dilemmas raised in these cases. Bruce Korf, MD, draws upon his experiences as a clinician and educator to highlight strategies used to teach medical students and residents about the integration of genomics and personalized medicine into clinical practice. He stresses in particular the necessity of learning resource management and the conceptual competencies needed to stay abreast of clinical utilities as the field continues to develop.

Two articles in this edition also discuss the paradox of using personalized medicine, a technology ostensibly developed to tailor therapies to the individual, to potentially derive conclusions about cultural and ethnic groups. First, MD-PhD candidate Tim Chang reviews a 2009 journal article investigating whether genetic factors in the disease course of systemic sclerosis could be correlated with psychological and behavioral measures and, subsequently, patients' perceived functioning. The second article, by Ramya Rajagopalan, PhD, and Joan Hideko Fujimura, PhD, uncovers the errors that can occur when racial or ethnic group membership is used to guide treatment decisions.

In the state of the art and science section, Aaron M. Lowe, PhD, reviews a central aspect of personalized medicine: technologies involved in the rapid and reliable detection of genetic sequences and mutations. Starting from the sequencing of the human genome, the article highlights some of the technologies in the pipeline, what their current limitations are, and their medicolegal implications.

The health law section extends the discussion introduced in the first case discussion. Shawneequa Callier, JD, MA, and graduate student Rachel Simpson examine the medicolegal protections and ramifications of the communication of genetic risk to the families of those with disease. Legal precedents, the authors say, are insufficient guides for clinicians about their duty to inform family members of genetic risk.

Because personalized medicine is still a developing discipline, policy makers must consider whether legal and ethical regulations will be needed as the field evolves. In the first of this issue's policy articles, Dov Greenbaum, JD, PhD, relates research on personalized medicine therapeutics to past policy on developing therapeutics for orphan diseases. His contribution delineates how government and private business can work together on regulation, privacy laws, and governmental incentives that will allow industry to grow responsibly and cost-effectively.

In the second policy contribution, Wendy Foth, Carol Waudby, and Murray Brilliant, PhD expound on the topic of biobanking that was brought up in case 3. Using their combined experience with the Marshfield Clinic's Personalized Medicine Research Project, they discuss Department of Health and Human Services-issued certificates of confidentiality that biobanking organizations are encouraged to obtain prior to amassing large collections of personal genomic information. This article highlights the ethical and practical advantages these certificates offer to patient and researcher alike.

Finally, Sara Wainscott, MFA closes out this issue on personalized medicine with a poem. In a ghazal, she traces the historical, political, scientific, and metaphorical aspects of the genome, weaving together a scientific fabric that touches upon important contributions and advancements in the field that are transforming personalized medicine from dream to reality.

This month's issue faced a unique challenge of commenting on the ethics of a field that is in its infancy and only starting to appear in clinical practice. Although some might consider the treatment premature, we consider it essential to subject the emerging concerns to scrutiny and incorporate our answers into medical decision making. We consider this the beginning of an ongoing discussion about using genomes to explore disease and define—or redefine—the individual.

Byram H. Ozer, MD, PhD
PGY-2, Neurology
University of California, Los Angeles
Los Angeles, California

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ETHICS CASES

Genetic Testing: Clinical and Personal Utility

Commentary by Rachel A. Mills, MS, Susanne B. Haga, PhD, and Geoffrey S. Ginsburg, MD, PhD

Dr. Orson is a family practice physician who has been treating Michael since he was born. He knows Michael's parents and siblings, having been their family doctor for nearly 30 years. He is also intimately familiar with Michael's family history: 3 members of his family in their 30s and 40s have suffered sudden cardiac death. Michael is now 22 years old, 10 years younger than his uncle was when he died of this cause. Michael is therefore vigilant about clinical surveillance of his overall health, but tends to avoid the subject of his family history altogether. He has, however, happily shared with Dr. Orson news of his recent marriage and his desire to start a family.

In preparation for Michael's first office visit since his marriage, Dr. Orson has done some research and found a genetic testing kit that examines a 5-gene profile of known inherited mutations that can lead to arrhythmias or death. Dr. Orson believes that the testing will either alleviate Michael's anxiety or allow him and his wife to prepare for possible cardiac complications.

Dr. Orson enters the exam room to find Michael accompanied by his wife Susan, who announces that they are expecting their first child. Dr. Orson congratulates them and inquires after the course of the pregnancy. Then he turns to Michael to continue the annual check-up. After giving Michael a clean bill of health, he brings up the topic of genetic testing and encourages Michael to submit a sample to test for the known channelopathies. Michael's mood changes; he becomes upset and angry about the suggestion.

"I'm about to become a father and you're telling me to take a test that might announce a death sentence?" Michael eventually says.

"I think it would be valuable information to know so we could initiate treatment or, at worst, prepare your family to anticipate...complications. We have ways of better predicting likelihoods of serious diseases now; why not use that information to prepare yourself appropriately?" Dr. Orson retorts.

"Why would I want to know that I might die soon? Can't I just live my life like everybody else, without thinking about my own mortality?" Michael responds.

Dr. Orson insists, “But the test could also provide reassurance, and think of your family and how they should prepare. I’m confident that if this testing had been available for others in your family, they would have gotten it. I really think you should consider it, for your good and the good of your family.”

Michael curtly thanks Dr. Orson for his time and the check-up and leaves the appointment. As Susan prepares to follow, Dr. Orson asks her to see if she can talk with him at home about the testing.

Commentary

In the past two decades, a number of genes have been found to be associated with dysfunctions of ion channels in cells (channelopathies) that can lead to sudden cardiac death. Testing is available when clinical symptoms, abnormal ECGs, or family history are present. Familion [1], GeneDx [2], and Correlagen [3] are commercially available genetic testing panels for mutations underlying channelopathies, cardiomyopathies, and other lethal cardiac disorders. Testing is also available through medical and research facilities [4].

With the identification of several causative genetic variants and testing platforms such as Familion, it is now the standard of care to discuss genetic testing for channelopathies, particularly for patients with a significant family history like Michael’s [5, 6]. However, the utility of genetic testing may be limited—only some genetic variations in one disorder, long QT syndrome (LQTS), can guide therapy [7], while the clinical recommendations are not yet well-defined for asymptomatic people with genetic mutations associated with other channelopathies, such as short QT syndrome or Brugada syndrome.

The case of Dr. Orson and his patient Michael raises questions about the management of patients with a family history of sudden cardiac death. One is the timing of Dr. Orson’s discussion about genetic testing. Given Dr. Orson’s long-time care of Michael and knowledge of the family history, a discussion about genetic testing might have best been had earlier. Though it is possible that Dr. Orson might have not had the knowledge or access to such testing, he could have referred Michael to a genetic specialist who would be more knowledgeable about familial channelopathies and options for genetic testing. Unfortunately, like many primary care physicians today, Dr. Orson may have been hindered by lack of education about genetics and genetic testing or lack of access to genetics professionals [8].

The primary ethical dilemma is that Dr. Orson is stuck between the duties of beneficence and nonmaleficence on the one hand and respect for patient autonomy on the other. These three principles are central to medical ethics. Beneficence means promoting good and nonmaleficence is the avoidance of harm; respecting patient autonomy is about honoring and promoting patients’ wishes, values, and preferences for health care. Dr. Orson recognizes that if Michael doesn’t have this testing, he may be missing the opportunity for treatment. Further, Dr. Orson is concerned about the health and well-being of Michael’s unborn child and any future children.

To find balance between these competing ethical duties, it is important that Dr. Orson and Michael consider the clinical utility, as well as the personal utility, of the test. Clinical utility is an intervention's usefulness in changing clinical outcomes, while personal utility takes into account things like psychosocial effects, family planning, lifestyle changes, future decision making, and the value of the information to the patient [9].

Dr. Orson's situation is not an uncommon one, especially concerning genetic tests with limited clinical utility. The potential "burden of knowledge" often influences a patient's perception of personal utility, as is commonly seen by geneticists and genetic counselors working with families affected by diseases like Huntington, Alzheimer, and some cancers. There are currently no treatment or preventative measures that patients at increased risk of these diseases can take; thus, genetic testing would not have significant clinical utility. The primary benefits of this testing would be personal: genetic testing can provide knowledge about disease risk for the patient and family members and inform life and end-of-life decisions. The risks associated with testing for diseases with no clinical utility include psychological burden and genetic discrimination—although the Genetic Information Nondiscrimination Act (GINA) protects patients from changes in health insurance or employment, it does not cover life insurance or disability [10].

It is difficult to compare the risks and benefits of genetic testing in cases like Michael's; each risk or benefit can have a different "weight" for every patient. Even people within the same family may make different decisions about testing based on how they weigh these risks and benefits.

Testing Michael for channelopathies may have some clinical utility, unlike testing for Huntington or Alzheimer diseases. With a genetic diagnosis of long QT syndrome, for example, there would be the possibility of treatment with beta blockers and risk reduction by lifestyle modification. However, in Michael's situation the benefits of genetic testing are uncertain. It is unclear which hereditary channelopathy is affecting Michael's family. Without this knowledge, one cannot know whether Michael's genetic test would yield clinically useful information. If a symptomatic family member were to undergo genetic testing to identify the underlying mutation, the type of channelopathy would be specified. Then Dr. Orson and Michael would have a better understanding of the clinical utility of genetic testing for him. However, as Michael is already "vigilant about clinical surveillance of his overall health," he would probably find that genetic testing has limited clinical usefulness if testing of another family member revealed the familial syndrome was not treatable.

Conclusion

Though it is important that Dr. Orson consider the implications of genetic testing, ultimately the decision is Michael's. A legal and ethical precedent has been set recognizing patients' right *not* to know their genetic risk for diseases [11]. The

decision about genetic testing is a personal one that is influenced by a number of factors that a health care professional may or may not be able to appreciate completely. The patient will likely take into account the perceived treatability and preventability of the disease as well as a perception of his or her own personal risk [12]. Given the possibility of minimal clinical utility, the decision hinges on Michael's view of the test's personal utility.

It may be beneficial for Dr. Orson to refer Michael to a genetic counselor or a geneticist who is trained to discuss such testing with patients. Genetic counselors have a central ethos of "nondirectiveness" [13]; counselors seek to provide the patient with the information necessary to make an informed decision. Genetics professionals may also be able to determine which channelopathy is affecting Michael's family by doing a thorough review of his family history, thereby informing the decision further.

Dr. Orson may also consider bringing up genetic testing to another family member, perhaps someone who has been affected with symptoms of a channelopathy like syncope or who has an abnormal ECG. Genetic testing is most informative when performed on someone affected by the disease in question [14]. Once a concrete diagnosis is made within the family, Michael may reconsider testing, particularly if treatment options are available or he is interested in the possibility of ruling out the presence of the mutation.

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Further Reading

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Rachel A. Mills, MS, is a clinical research coordinator and certified genetic counselor at the Institute for Genome Sciences & Policy at Duke University in Durham, North Carolina. She received her MS in genetic counseling from the University of North Carolina at Greensboro. Her primary research interests include public and professional genetics education and the use of genomics in health care.

Susanne B. Haga, PhD, is an associate research professor at the Institute for Genome Sciences & Policy and Sanford School of Public Policy and the director of education and training at the Institute for Genome Sciences & Policy, all at Duke University in Durham, North Carolina. She received a PhD in human genetics from the University of Maryland. Her research interests focus on the translation of genomic medicine, particularly pharmacogenetics, and the legal, regulatory, ethical, educational, and social implications of genomic research and applications.

Geoffrey S. Ginsburg, MD, PhD, is the founding director for genomic medicine at the Institute for Genome Sciences & Policy, the founding executive director of the Center for Personalized Medicine, and a professor of medicine and pathology at Duke University in Durham, North Carolina.

Related in VM

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[Duty to Warn At-Risk Family Members of Genetic Disease](#), September 2009

[Familial Genetic Risk](#), June 2005

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ETHICS CASES

Informed Consent for Biobank-Dependent Research

Commentary by Jeffrey R. Botkin, MD, MPH

Dr. Hundt is a physician at a major research hospital. He is visiting a new patient, Mr. Clifton, who was recently admitted to the hospital for right upper quadrant pain suggestive of gallstones and cholecystitis. Dr. Hundt checks in with the patient to examine him and to explain what the course of hospitalization will be. The patient appears ill, but is alert and oriented. “We will have to draw blood to check some basic labs and to see if you have any possibility of infection,” Dr. Hundt explains. Mr. Clifton nods in understanding.

“I do want to mention to you a program of ours that has been approved by our IRB, which oversees human subjects research,” Dr. Hundt continues. “When obtaining blood samples for labs, we often have leftover blood and tissue. Because we have many researchers studying and developing therapies for genetic diseases, we are attempting to build up our database of genetic material to study population trends and genetic variations of disease. We have therefore established a program for banking leftover blood in our DNA database, in conjunction with basic demographics and medical information obtained from your medical record. We extract the DNA and make the information available to our researchers. Your name and identifying information are removed, and our researchers sign a confidentiality form promising that they will not try to reidentify the source of any genetic specimen.”

“Can you tell me more about what kinds of research the samples are used for?” Mr. Clifton asks.

“The spectrum of research varies across disciplines and disease systems, and the specimens will be used for as-yet-undetermined projects.”

Dr. Hundt gives Mr. Clifton a brochure. As Dr. Hundt is leaving, Mr. Clifton asks if he has to sign anything before the lab comes. “No need, Mr. Clifton. The specimen will be automatically entered into our database without any further action from you,” Dr. Hundt explains. “If you choose not to participate, there is a form at the end of that brochure. Please give that to the phlebotomist and that will let us know not to send your blood to the biobank.”

Commentary

This simple vignette illustrates a surprisingly complicated problem in contemporary biomedical research: should patients be asked to contribute their data and residual tissues to research and, if so, how should they be approached? Biobanks are proliferating and high-volume clinical services are being used as sources of tissues and data for research purposes. Biobanks linked with electronic medical records can be powerful tools for identifying biological correlates of health and disease. Much of the work in this domain is genetic, with the intent to identify DNA-sequence variations associated with disease. But human tissues are potentially valuable for a wide range of studies involving environmental agents, infectious diseases, protein biology, and epigenetic factors. The challenge is how best to acquire large numbers of samples of various types.

A central ethical concern in the conduct of research is the protection of participants from harm. In the biobanking context, there may be harms from the removal of tissues to begin with, such as blood draws or biopsies, but these are usually minor or otherwise justified for clinical purposes. The primary risks associated with this type of research arise from the potential for a breach in privacy to cause stigma or discrimination for the tissue source. Fortunately, to date, there have been no published cases of individual harm arising from biobank-dependent research despite the millions of specimens stored and tens of thousands of studies performed.

So why the controversy? Contemporary concerns fall into at least three domains. First, biobank research is often conducted without the knowledge or consent of those whose tissues are banked. Second, patients and research participants are worried about potential harms from this type of research, and studies show that many want some control over research uses of their tissues. Third, there are potential harms to particular social groups that need to be more fully explored.

The Federal Regulations

The federal regulations governing human subjects research permit research on banked tissues without informed consent in several circumstances. The regulations were established to protect human subjects, defined in the regulations as individuals who interact with investigators or whose identities can be readily ascertained by the investigator [1]. Research using tissues or data that is identifiable is considered human subjects research. Research with tissues or data that are “deidentified” or “anonymized” is not considered human subjects research and therefore can be conducted without oversight from an institutional review board (IRB).

In the case example, Mr. Clifton’s tissue or data can be used by investigators for a wide range of studies without Mr. Clifton’s knowledge or consent as long as the investigators cannot readily determine that the source of the tissue or data is Mr. Clifton. Of course, the tissue donor often gives permission for the original acquisition of the tissues, either through a clinical consent or a research consent process. But subsequent research projects need not re-obtain his consent, even if the research goals are not consistent with the original consent [2]. So if Mr. Clifton

agreed to have his tissues used for research on liver diseases, subsequent use on, say, diabetes research, would be acceptable under the regulations as long as the diabetes investigators could not readily identify Mr. Clifton.

In this regard, the regulations are not consistent with the simple ethical expectation that people live up to their agreements. To the extent that consent forms and processes are explicit about the intended use of the tissues, it is ethically problematic to use the tissues for other purposes, even if the risk to the tissue donor is minimal or nonexistent. There has been an active discussion at the federal level about whether the regulations should be changed to stipulate that uses of tissues and data should be consistent with (or at least not inconsistent with) the informed consent language.

A second scenario in which consent is not necessary is if the IRB waives the requirement for consent. Federal regulations permit a waiver of consent if four criteria are met: (1) the research is deemed to carry minimal risk, (2) the waiver would not adversely affect the rights and welfare of the participants, (3) the research would not be practicable without a waiver, and (4) the research participants will be informed later of the research, when appropriate [3].

In the context of biobank-dependent research, the key criteria are whether the research is considered minimal-risk and whether it is practicable to obtain consent from the tissue sources. As noted, the historical risk associated with this type of research is so low that IRBs often consider it to be minimal-risk unless the information involved is particularly sensitive. IRBs often determine the “practicability” question by the number of tissues involved and the nature of any ongoing connection between the research institution and the tissue sources. If the study involves a small number of identifiable specimens recently acquired from patients in a particular clinic, then the IRB may decide that seeking consent for the new use is feasible and appropriate. If the research is using hundreds of samples acquired over years, then the IRB may determine that it is not practicable to recontact such a large group.

The case example illustrates a situation in which tissues are being acquired for clinical uses but with foreknowledge that any residual tissues will be stored for research purposes. Despite the fact that patients are in the hospital or clinic while the tissues are acquired, an IRB may determine that a detailed research consent process can be waived based on the criteria noted above or decide that a simpler approach, like notification of research use with an opt-out provision, is an acceptable protection of patient autonomy.

The scenario in the case example is entirely consistent with the regulations governing human subjects research. Further, to the extent that a large volume of biomedical research is being conducted on residual clinical tissues without any notification of those whose tissue was used, the notification with an opt-out provision actually meets a higher ethical standard than many programs support. We can hope that clinicians will do a better job than Dr. Hundt of offering a simple

explanation in lay language, but the approach per se is entirely consistent with contemporary regulatory standards.

Public Expectations

The larger problem is that contemporary standards regarding waiver of consent or the use of deidentified specimens is not consistent with what many people want and expect. Those of us in the biomedical research enterprise have good reason to believe that this research is essentially harmless, but members of the general public don't have reasons to believe this or trust us. Further, many people want some level of control over their tissue simply because it is their tissue.

Surveys of the general public consistently show that people want some choice in research uses of residual clinical tissues and aren't supportive of the current lack of transparency [4]. As a concrete example, controversy arose over the research use of residual newborn screening bloodspots in the states of Texas and Minnesota. Privacy advocates became aware that a number of states, including Texas and Minnesota, saved leftover bloodspots following mandatory newborn screening and made these spots available to qualified investigators without the knowledge or consent of parents [5]. Following lawsuits in both states over the lack of parental permission, millions of specimens were destroyed, and both states are moving toward systems that are more transparent with parents.

So there is a mismatch between standards acceptable to investigators (and research oversight systems) and to patients for the perceived risks associated with biobanking and decision making by patients. Investigators are focused on the value of the research and see minimal risks, while patients are concerned about risks and expect to participate in decisions about the use of their tissues.

The other potential mismatch between standards and expectations is in the respective perceptions of "practicability." Many who are not in the biomedical field think it is relatively straightforward to ask people about the management of their tissues. Those on the research side perceive enormous complexities in trying to engage thousands of individuals in a meaningful fashion about relatively complex or abstract decisions. Patients who are sick, anxious, eager to please the doctors, and unschooled in even basic scientific facts and terminology often are not in a position to understand and deliberate about biobanking choices. At best, one might expect the sort of technical and perfunctory presentation by Dr. Hundt in the case example.

From an ethical perspective, the key question is whether individuals are informed about their choices regarding research use of tissues and data and whether they can effectuate a choice without undue burden. In my opinion, whether the approach to choice is an "opt-in" with a signature or an "opt-out" is a secondary issue.

Group Harms and Wrongs

The third set of concerns arises from fears of harm or wrongs to social groups rather than to individual research participants. Let's imagine that all identifiers are stripped

from Mr. Clifton's sample before it is made available for research. The de-identification of the sample significantly reduces or eliminates the risk of harm to Mr. Clifton as an individual. Yet imagine that Mr. Clifton is from a Native American tribe and that his group identification remains with his sample and an investigator wishes to use the specimens from members of his tribe in the biobank to assess historical migration patterns of his tribe across continents. Mr. Clifton might well object to such research because it undermines traditional tribal origin stories. Has Mr. Clifton been harmed by such research? Perhaps not in a tangible way, but we might conclude that he has been wronged, as have other members of his tribe, unwilling participants in research to which they object. This hypothetical scenario is based on the controversy over specimens that were acquired from the Havasupai Indians for diabetes research but subsequently used for a variety of other projects [6].

The federal regulations governing human subjects research were designed to minimize harm to individuals. The regulations do not address the possibility of group harms, although IRBs can set higher standards than the federal regulations and may choose to attend to this potential problem.

Conclusion

Biobanks have become essential tools for contemporary biomedical research. Yet there is clearly much creative work to be done to bridge the divide between patient understanding and expectations and the efficient conduct of research using large sample sets. Earning and maintaining the trust of the public is essential to allow valuable research to move forward.

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Jeffrey R. Botkin, MD, MPH, is a professor of pediatrics and medical ethics and associate vice president for research at the University of Utah in Salt Lake City.

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Virtual Mentor

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ETHICS CASES

Genetic Profiling of Medical Students

Commentary by John Mahoney, MD

Dr. Shepherd is a medical school professor charged with incorporating pharmacogenomics and genetic testing into her medical genetics curriculum for first-year students. To personalize the experience, she partners with a direct-to-consumer genetics testing company, for which she has consulted, to develop a modified and discounted genome test that examines four genotypes for nondisease states, including genes involved in the metabolism of certain macronutrients, medications, and alcohol. With approval from the medical school administration, the cost of the test is rolled into each student's tuition and notices are sent to all incoming medical students informing them of the study and requesting their informed consent. Once consent forms are received, the testing organization will solicit the specimens. The deidentified reports will be filed with the medical school's genetics department and made available to the participating students for reference and discussion during their medical genetics course.

Several weeks after the notices are sent out, Dr. Shepherd receives an e-mail from Lacy, a newly accepted student who is finishing a master's in genomic sciences. Lacy writes that, though she lauds the intention behind the project, she has objections to its implementation. She worries that medical students may feel pressured into participating in the project for fear of adverse academic consequences. She voices concerns about discovering and revealing genetic information, even if the information is relatively benign, and especially without the appropriate counseling. She is particularly concerned with the lack of clarity about what other student information might be collected and how privacy will be protected. She ends her communication by saying that she will probably participate if she can get her questions answered but worries that other incoming students may not fully appreciate the implications of the project and may not feel comfortable obtaining appropriate information or abstaining.

Commentary

This case describes a plan by a creative professor to stimulate student interest in studying genetics by using results from students' own specimens for analysis and discussion. A thoughtful student raises concerns about consent, coercion, and privacy. This commentary addresses the nature of the genetic profiling tests and ethical considerations for the instructor and school and identifies some unanswered questions about genetic screening.

Genetic Profiling Tests

The testing proposed here is a subset of the typical personal genomic testing that is marketed to consumers. Unlike clinical testing for a specific monogenetic disease, in this approach the tests typically result in profile information about the relative risk of developing a condition. The profile results are of limited clinical utility, particularly if they are interpreted without a correlation to a patient's overall health and medical history and if they yield a relative risk that is indistinguishable from that of the general population [1]. Consumers are not usually given in-depth, personalized pre- and posttest counseling or interpretation assistance as they would be when working with medical geneticists.

There are a range of motives and justifications for genetic profile testing. Proponents can reasonably argue that any information about current health or future diseases could potentially be useful, particularly if it can be obtained noninvasively and at modest cost. Businesses that sell testing kits or services have been effective in marketing them to the general public, but the benefit of such testing is nowhere near as clear as that of diagnostic testing in the clinical setting.

Ethical Considerations

The ethical concerns in the scenario include loss of privacy, an increased risk of future harm, coercion to consent, testing without counseling, and the consequences of how students are billed for the testing. Among these, it is useful to organize them in terms of their magnitude, related to the consequences of the worst possible or likely outcome.

Loss of privacy. Using this approach, a student's privacy might be regarded as being at risk of real and lasting harm. Today's world is replete with scientific discoveries, but also with security breaches, malevolent hackers, cyberattacks, and industrial espionage. Even without an overt breach of security, some number of staff at the testing company will have access to the students' results. These factors, alone or in combination, could counteract the measures taken to protect the students, which compels us to consider the possible impact.

The consequences of a privacy breach fall along a spectrum. At minimum, it invalidates the trust placed in the professor, university, and testing company. Although the proposed profile will not test for disease states, a student could be identified as being destined to develop a significant metabolic condition (the case mentions alcohol metabolism, for example). Thus, loss of confidentiality could place the student at risk for a gamut of discriminatory outcomes or stigmatization, including employment and insurance discrimination. Legal statutes are in place to help prevent this type of discrimination, but statutes cannot shield a person from all possible harms [2].

New gene-disease associations are being discovered continually, so a gene or sequence that is now thought to be inconsequential may in future be found to be diagnostic or predictive [1]. There is risk, therefore, that a student may ultimately be

confronted with genetic information that he or she had not chosen to know. The psychological impacts of such possibilities, including anxiety about how a result could affect career and family, adds to the stress that medical students already face.

Possible future knowledge of harm. Medical education often includes learning activities in which students' bodies are involved—students often practice physical examination skills on each other, examine their own blood or urine, or, as ultrasound instruction is introduced, practice on each other. Any of these activities could reveal a significant abnormality, such as a previously undetected blood dyscrasia or a congenital renal malformation. One difference between these activities and performing genomic screening testing is that the genomic testing generates a permanent third-party record that may later affect the student. The anonymity of the testing leaves students in the dark about what information is recorded about them and opens the door for anxiety about the unknown. While a basic science professor might perceive this as a minor and dismissible concern, it may not be trivial for a student.

For the school and professor, there are ethical implications to gathering this data while not being in a position to readily share any vital findings, now or in the future. The implications of what we may be able to do with this information could be far-reaching. An uncertain and changing future should at least be anticipated and consideration given to protecting the students from future harm.

For example, in this case, the professor believes the tests are for nondisease states. Interpretations of genetic testing results are already being revised as new gene-disease associations are discovered; in the not-too-distant future, one of these patterns may be found to be inextricably linked to a serious disease condition [3]. In a typical clinical practice, a geneticist might become aware of a new gene association, prompting a review of existing data and records. If this review identifies a patient result on file with the newly-significant finding, the practice contacts the patient.

Such reinterpretation could be done with data already used by the professor without the original specimens or costly reprocessing. A curious professor might choose on his or her own to review the data on hand to see if it revealed a profile with the newly significant finding—but it is not clear whether the professor or school has the same obligation as a clinical practice to notify if a significant abnormality surfaces.

An additional dilemma is how to communicate with the person with the abnormal result, since the professor does not have individually identified results. Is there an ethical or moral obligation to contact all students to advise them that they *may* be at specific risk and should proceed to be individually tested? This would appear to be desirable, but it would be fair to ask if it is realistic. At a minimum, this type of situation should be anticipated and plans made for handling it, which should be explained in the informed consent process. For example, if the university and professor decide that they will not undertake profile reinterpretation even as clinical knowledge evolves, this should be disclosed to the students.

That the professor and the entire class will have the set of data from the student testing raises another concern. It is possible that future discoveries will reveal new linkages between this genomic data and physical or ethnic characteristics (for example, between “macronutrient gene 1,” eye color, and ethnic background). These linkages may be sufficient to identify individuals, thus breaking the confidentiality that had been promised [3].

Coercion to consent. Lacy is justifiably concerned about being coerced to consent. Students generally understand the preciousness of their place in the medical school class and may perceive that their success is dependent on the goodwill of those with power (the professor and school administration). Given that students are totally dependent upon their professors and administrators to succeed in medical school, concern over the impact of declining to participate is entirely reasonable.

With this perceived or real vulnerability and significant power differential, substantial safeguards should be in place to prevent the professor and school administration from knowing who has opted out. Under the circumstances, there is no opportunity for students to ask consent-related questions, let alone do so in a safe environment. These young students are vulnerable to feeling pressured to participate along with the group, perhaps more so than would a group of experienced physicians engaging in similar coursework as part of a continuing education program. One might wonder if the school would even attempt to push faculty into this type of activity, in contrast to taking student participation for granted and giving only minor attention to a consent process.

Absence of counseling. Beyond coercion concerns, the consent process falls far short of accepted contemporary practices for counseling prior to genetic testing. In clinical genetics practices, extensive counseling provides patient with a solid foundation for making thoughtful and well-informed consent decisions [1]. In this case, this in-depth counseling is unavailable and impractical. The students are being treated like consumers who have volunteered for testing. Yet these students are being strongly encouraged to be tested by medical professionals at a medical school—entirely unlike consumers.

The lack of appropriate counseling may suffice to make proceeding with genomic testing unethical. An alternate viewpoint that the professor might voice is that, since no personal results will be reported to the student, there is no need for counseling of any sort—no risk of personal adverse findings, so no risk of adverse psychological or other impact.

Financial matters. An additional concern raised in this case is that students are being compelled to pay for the testing as part of their tuition. It is not entirely clear if there has been a disclosure to the students that they will be paying for testing for which they may elect not to consent. Including the fee in the students’ bills without awaiting their consent communicates the professor’s and school’s overall attitude—

they seem to have together decided that the students will participate and will pay and that the consent from individual students is a mere formality that can be taken for granted.

This approach might be more acceptable if it did not involve medical testing. The nature of the testing significantly changes the degree to which students must have an opportunity to exercise autonomous decision making, and the school must be sure it is acting in the students' best interests. Alternatively, if students were truly given the option of choosing to be tested, and only paying if they were being tested, the students' views on testing might be influenced. Having to pay an additional, optional fee might cause some students to opt out for financial reasons and others to feel more invested in the activity than if it were free. An optional fee might also cause them to think more seriously about the testing before consenting to participate.

Advice

This case sheds light on a broad range of ethical considerations associated with genomic profiling testing, and aspects of the power differential between educators and their students. Though the professor is probably attempting to provide a well-intentioned stimulus to learning, the potential negative consequences are many and the educational benefits are unclear. An educator might ask why this professor should bother with testing this class of students if the results are anonymous. It is not entirely clear whether it will really enhance learning. As proposed, students must pay for the tests, and there is the possibility that the tests could produce data that will cause alarm or harm, as described above. Yet no single party benefits from the testing, except perhaps the testing company. Considering that the professor has a prior consulting relationship with the testing company, there is the possibility that the professor has a conflict of interest that should be disclosed or avoided altogether [4]. If I were mentoring the professor, I would give advice on several aspects of the plan.

In general, I would urge Dr. Shepherd to pause and reconsider the proposed plan from a student's point of view. I would guide her to seek an alternative approach that does not place the students in an untenable position or that employs confidential, sensitive data when a safer alternative is available. The most basic alternative is to use existing data rather than test the students.

If testing were to proceed, the professor should arrange to work with a testing company with which she has no financial connection, rather than one she served as a consultant. Alternatively, she should provide the medical school and participating students with a clear disclosure of the possible conflict of interest. A process must be arranged in which the students have unimpeded access to thorough pre- and posttest counseling. The consent process must permit students to accept or decline testing without any possible reprisal for choosing to not be tested. This should include preventing faculty who may be grading the students from having knowledge of whether they consented to testing. To provide all possible security for their information, the professor and testing company should use anonymous sample submission and results retrieval, comparable to the way some HIV testing programs

are conducted. The professor and medical school should provide students with information about how they will communicate with students if there are relevant discoveries in the future.

If I were speaking with Lacy, my advice would include referring her to the dean of students or another student advocate for assistance with a tactful method of declining to participate. Students in this case may face a no-win scenario and be forced to choose which way they wish to lose.

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John Mahoney, MD, is associate dean for medical education and an associate professor of emergency medicine at the University of Pittsburgh School of Medicine in Pennsylvania. His academic interests focus on innovation in medical student education and on improving the connections between students, faculty, and patients.

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MEDICAL EDUCATION

Genetic and Genomic Competency in Medical Practice

Bruce Korf, MD, PhD

The principles of Mendelian and molecular genetics have long had a place in the preclinical medical curriculum, but clinical applications of genetics have been barely visible in the clinical training of medical students, residents, and postgraduates. Undoubtedly this absence reflected a perception that the focus of medical genetics is rare disorders, so most medical professionals could get by with minimal exposure to the discipline. Since completion of the sequencing of the human genome, the power of the genetic—and now the genomic—approach has increased enormously, providing new tools to diagnose and even treat both rare and common genetic conditions. Those at all levels of training must now gain competency in a complex and continually evolving area. I will try to set forth some principles that may be helpful in navigating this new area.

Principles

1. Focus on competencies, not knowledge. The genome can be a source of endless fascination—how is it possible to encode all of the information necessary for a human to develop in three billion bits of information that can be folded into a microscopic structure?—and the technology is dazzling—how is it possible to decode this information in a matter of days (soon, hours)? The practicing physician, however, is not going to be sequencing the genome or interpreting the raw data any more than he or she now analyzes raw data from blood work or MRI scans.

This leads us to the competencies—what should the physician be able to do using the genetic and genomic approach? Physicians need to be able to respond to an abnormal newborn screening result; to know when and how to arrange genetic testing and consultation to help establish a diagnosis; to obtain and interpret family histories so they can inform patients about risks and arrange for genetic testing or consultation to clarify that risk; to use pharmacogenetic testing to customize drug choice and dosage to an individual's physiological needs; and to interpret the results of genome-wide testing for risk of common disease.

Competencies in these areas have been defined for physicians at many levels. The Association of American Medical Colleges (AAMC) and Howard Hughes Medical Institute have tackled premedical and medical genetics education with broad competencies that leave a lot of room for faculty to add detail [1, 2]. The AAMC Medical School Objectives Project provided more detailed objectives in genetics [3], and the Association of Professors of Human and Medical Genetics objectives went into even finer detail [4]. The National Coalition of Health Professional Education in

Genetics [5] has developed core competencies in genetics for all health professionals and is developing a genetics curriculum. Detailed competencies have been written for the medical geneticist by the American College of Medical Genetics [6] (yes, it is possible to do a residency in medical genetics, recognized by the American Board of Medical Specialties and accredited by the Accreditation Council of Graduate Medical Education), guidelines have been proposed for internal medicine residency education [7], and the American Academy of Pediatrics has launched a Genetics in Primary Care Institute aimed at the continuum from residency to independent practice. All of these efforts, of course, must take account of the fact that genomics is quintessentially a moving target; most of the competency projects mentioned above predated the era of whole-exome/whole-genome sequencing, which has only been possible on a clinical basis for the past year or two yet is likely to become the mainstay of testing in the next few years.

Competencies are not acquired by attending lectures or reading books. These modes of instruction can provide a foundation, but competency is achieved by doing. To some extent, the road to competency may be paved by experiences in problem-based learning or simulation, but increasingly genetics and genomics will be incorporated into day-to-day teaching on inpatient and outpatient rotations for students and residents and postgraduate experiences for those in practice. There may be a need for immersion courses for practicing physicians to help them quickly acquire the basic skills necessary for incorporating genetics and genomics into their practices.

2. Learn to use point-of-care sources of information and decision support tools.

Genetics and genomics deal fundamentally with information—indeed, the genome is the biological store of information necessary to build a functioning organism. With more than 20,000 genes and even more regulatory sequences, all of which interact in networks, the genetic data exceeds human processing capability. Just as it is impossible to fly a modern jet airplane without computer assistance, it is becoming impossible to practice medicine without the same. This is not to devalue the human interaction, which always has been and always will be the core of the medical encounter between physician and patient. Rather, it enriches that encounter by giving the physician an unprecedented store of information and tools to improve outcomes.

There are several online sources of crucial genetic information. Some are intended for use by medical geneticists, but others are useful to all practitioners. Online Mendelian Inheritance in Man [8] is the authoritative catalog of human genetic variants, including the clinical characteristics of associated disorders. GeneReviews [9] is an online compendium of indispensable peer-reviewed summaries of a wide variety of rare and common genetic disorders. Its parent site GeneTests [10] is a database of genetic testing laboratories. The new NIH-run Genetic Test Registry [11] is another database that provides information on laboratories that offer genetic tests.

Pharmacogenetic testing will increasingly be used to customize both drug choice and dosage [12]. Most likely, interpretations of test results will be embedded in electronic prescribing systems; physicians will understand that drug dosage may

need to be modified according to genotype, but the calculations are likely to occur behind the scenes. The role of genomic testing to determine risk of common diseases remains uncertain at present; so far, most genetic markers are only modestly predictive of disease risk. Nevertheless, some individuals are being tested for a million single nucleotide polymorphisms at a time (i.e., variations at a million DNA loci), in some cases on a direct-to-consumer basis [13]. Physicians must be able to respond to the results of these tests and help patients use the information wisely.

3. Counteract misinformation about genetics and genomics. Most people have at least an intuition about genetics—it's widely recognized that children take after their parents—yet are likely to have misconceptions. One is the notion of genetic determinism—that your destiny, at least regarding your health, is written in your genes. This may be more or less true for some conditions, such as cystic fibrosis or Huntington disease, but as we turn attention to more common multifactorial disorders, gene-environment interactions become more important and the ability to predict disease based on genetic testing less powerful. Moreover, even rare genetic conditions may be subject to modification by changes in lifestyle, environment, surgery, or medication. Medical therapies are being developed for a growing number of genetic disorders previously thought to be untreatable, and genetic testing is playing a major role in assessing familial risk of cancer [14] to provide approaches to risk reduction.

Accordingly, there is a second misconception that genetic information is inherently more sensitive than other types of medical information and requires correspondingly greater protection. This may be fueled by the notion that genetic testing can diagnose risk of disease in healthy people and that risks may apply to family members as well as to those being tested. Avoidance of genetic testing for fear of misuse of the information will deprive individuals of major potential benefits, which was the rationale for passing state and federal laws [15] to protect people from discrimination in employment or eligibility for health insurance based on their genetic information. At the same time, other kinds of test results, including those for risk factors such as cholesterol or infections that can be transmitted to close contacts, may be just as sensitive as genetic test results.

A third misconception is that genetic testing is always expensive and not covered by insurance. In fact, genetic testing varies widely in price and often may provide a shortcut in an otherwise very costly diagnostic odyssey. As with any medical procedure, it is always wise to check on a patient's specific insurance coverage, but many forms of diagnostic and predictive tests are covered with appropriate clinical indications.

Conclusions

Some have complained that the benefits of sequencing the human genome were oversold and that medical applications have been slow to develop. The complexity of translating genetics and genomics information into usable knowledge should not be underestimated, but the pace of change in genomic medicine is accelerating. It cost

more than \$1 billion to sequence the first human genome in 2003 [16]; now a human genome can be sequenced for a few thousand dollars, and the cost is still falling. Clinical genome sequencing has already begun and is likely to be a mainstay of diagnostic testing within the next few years [17]. The era of genomic medicine has begun—our patients expect us to be competent in using this powerful approach to their benefit, and we must work now to insure that our trainees and professional colleagues are prepared for what is here now and what is to come.

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Bruce Korf, MD, PhD, is a medical geneticist who is board certified in pediatrics, child neurology, medical genetics, clinical cytogenetics, and clinical molecular genetics. He is the Wayne H. and Sara Crews Finley Professor of Medical Genetics, chair of the Department of Genetics, and director of the Heflin Center for Genomic Sciences at the University of Alabama at Birmingham. He is immediate past president of the American College of Medical Genetics and Genomics and president of the ACMG Foundation for Genetic and Genomic Medicine.

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THE CODE SAYS

The AMA *Code of Medical Ethics*' Opinion on Disclosure of Patients' Genetic Test Results

Opinion 2.131 - Disclosure of Familial Risk in Genetic Testing

(1) Physicians have a professional duty to protect the confidentiality of their patients' information, including genetic information.

(2) Pre- and post-test counseling must include implications of genetic information for patients' biological relatives. At the time patients are considering undergoing genetic testing, physicians should discuss with them whether to invite family members to participate in the testing process. Physicians also should identify circumstances under which they would expect patients to notify biological relatives of the availability of information related to risk of disease. In this regard, physicians should make themselves available to assist patients in communicating with relatives to discuss opportunities for counseling and testing, as appropriate.

(3) Physicians who order genetic tests should have adequate knowledge to interpret information for patients. In the absence of adequate expertise in pre-test and post-test counseling, a physician should refer the patient to an appropriate specialist.

(4) Physicians should encourage genetic education throughout a medical career.

Based on the report "Disclosure of Familial Risk in Genetic Testing," adopted June 2003.

Related in VM

[Genetic Diseases and the Duty to Disclose](#), August 2012

[Duty to Warn At-Risk Family Members of Genetic Disease](#), September 2009

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JOURNAL DISCUSSION

Personalizing Medicine: Beyond Race

Timothy Chang

McNearney TA, Hunnicutt SE, Fischbach M, et al. Perceived functioning has ethnic-specific associations in systemic sclerosis: another dimension of personalized medicine. *J Rheumatol*. 2009;36(12):2724-2732.

Considering the explosion in medical technology, from genomics and genetic biomarker testing to computerized imaging and detailed electronic medical records, personalized medicine may one day be common practice in our medical system. In “Perceived Functioning Has Ethnic-specific Associations in Systemic Sclerosis: Another Dimension of Personalized Medicine,” Terry McNearney et al. [1] found that “clinical, psychosocial, and immunogenetic variables had ethnic-specific associations with perceived functioning” in patients being treated for systemic sclerosis (SSc) [2]. The relationship of ethnicity both to the clinical, psychosocial, and immunogenetic variables and to perceived functioning raises ethical questions, especially if clinicians “personalize” treatment based on these findings.

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and internal organs, commonly preceded by autoantibody production and vasculopathy [3]. Although management of complications has improved, the median survival after diagnosis is 11 years [4]. Currently, SSc is incurable, and health-related quality-of-life (QOL) measures are important indicators of disease outcome [5-9].

Conclusions from Study

In this cross-sectional study, Caucasian, Hispanic, and African American patients with recent-onset SSc were assessed for perceived physical and mental functioning using validated surveys and a self-reported physical disability instrument. Perceived functioning scores were then tested for association with demographic, socioeconomic, clinical, immunogenetic, psychological, and behavioral variables. Among Caucasians, immunogenetics, fatigue severity, helplessness, and social support were associated with perceived functioning [10], while among African Americans and Hispanics, immunogenetics, autoantibodies, illness behavior, and helplessness were associated with perceived functioning [10]. This study is the first to identify associations between perceived SSc functioning and ethnically specific genetic markers and autoantibodies.

The authors draw various conclusions from their study. They modify a conceptual framework of health-related quality of life that was used for populations with HIV to

create their own model. This model hypothesizes that, while it is known that genetics influences SSc disease expression, symptom manifestation, and eventually QOL, genetics also influences a patient's ethnicity and cultural identity, which in turn influence socioeconomic status, social support, behaviors, and, again ultimately, quality of life [11]. The authors thus argue that genetic background contributes directly and indirectly to quality of life and that the contribution of culture to QOL may be modifiable [10]. Ethnicity, they say, should therefore be considered when designing personalized interventions to modify not only symptoms but also psychology and behavior [10].

Limitations

Alternative interpretations of the data are possible. The differences in perceived functioning for ethnic populations with a specific genotype may be a result of confounding variables. Moreover, comparison of these individual scores across ethnic groups has not been validated. For example, a lower individual score on social support may not necessarily mean that a person's ethnic group has lower social support than another ethnic group. It also remains to be seen whether modifying these perceived functions would have beneficial quality-of-life outcomes.

Although there are limitations to the study, it lends some support to the claim that genetics contributes to disease severity and ethnically distinct perceptions of disease-related physical and mental functioning. There are, of course, many ethical issues raised at the intersection of race, genetics, and disease response.

Race in medicine. Documenting race is considered helpful in medicine in many ways. In making differential diagnoses, for example, clinicians use evidence of higher-than-average probability of disease among members of racial or ethnic groups—such as Tay-Sachs disease in Ashkenazi Jews, sickle cell disease in African Americans, and cystic fibrosis in Caucasian Americans. Drug metabolism varies among groups classified by the term “race” [12], and race has been used in predictive models for determining appropriate drug treatment [13].

Using race and ethnicity to alert clinicians to greater likelihoods of certain health conditions became more controversial with the development of what was considered a race-specific drug. In 2005, the FDA approved isosorbide dinitrate/hydralazine (BiDil), a combination antihypertensive and vasodilator drug, specifically for African Americans. Major controversy ensued over whether a drug should be approved for use in a specific race since most drugs have long been tested on white subjects but not approved only for whites [14]. Moreover, approval of BiDil for African Americans was not granted for biological or genetic reasons—the proposed differences in mechanism of nitric oxide uptake in African Americans were never tested [15, 16].

Race-specific treatments are not an all-or-nothing phenomenon [17]. Not every person within a racial or ethnic group responds to a treatment in the same way. Suppose a given gene variation was more common in one group and led to a

statistically beneficial outcome for a drug among members of that group. Many people in another racial or ethnic group have the same gene variation. If drugs are approved only for the former group, people in the latter group would stand a lesser chance of benefiting from the drug.

Furthermore, the supposed effectiveness of race- or ethnic-specific drugs may backfire for pharmaceutical companies. To the degree that pharmaceutical companies target products for use by specific groups, they will have smaller markets [18, 19].

The conclusions of McNearney et al. can be stigmatizing. The danger of using race in such a fashion is that it may portray a racial group as genetically, socially, or behaviorally inferior [20]. Suppose, for example, that to optimize perceived functioning among those with systemic sclerosis, health care professionals offered behavioral and coping strategy support only to Hispanics and African Americans. Patients self-identifying in these groups could well see this type of personalized treatment as condescending.

Treatments based on group membership can also be clinically counterproductive. Those who would benefit from a treatment but don't fit "the profile" may receive insufficient care, and those who belong to a given group but don't have the relevant characteristic may receive unnecessary care. Hence, while race may sometimes be useful in the current state of medicine, overreliance on it may lead to ineffective, unjustified, unfair, and stigmatizing treatment.

Is race a biological concept? Until now, I have been talking as though race has biological meaning. There is clear evidence, however, that race is not a genetic concept [21, 22], and some would argue that it has no biologic basis [23]. Only 5-10 percent of genetic diversity is explained by one's membership in a given "race" [24-26]. In actuality there is as much or more genetic diversity within a racial group as there is between racial groups [17].

Race is more a sociopolitical concept than a biologic one. The concepts of race and ethnicity were not developed for scientific use but are popular concepts, which, in the United States, were made official for census taking by the Office of Management and Budget Race and Ethnic Standards [27].

Membership in race is defined differently across research studies, time, and geography. Most studies do not report how race information is obtained [28], e.g., self-identified or clinician determined, let alone standardize the process. The definition of race is also time- and geography-dependent [16]. How "black" and "white," for example, are defined in the United States has changed from the 1800s to the 1900s. Because race is identified by one's parents at birth and can be assigned by the medical examiner at death, a person may be born "black" but die "white" [17]. Geographically, a light-skinned person may be considered white in the Bahamas but

black in the United States. Inconsistencies in the definitions of race make its usage problematic at best.

Given the nonbiologic basis of race and its inconsistent definitions, should it be used at all? Some believe race should not be used in medicine and research [23]. They believe avoiding classifying people by race will help promote recognition of the heterogeneity within groups [28] and continuing its use will derail true genetic research [19]. Focusing on racial health disparities also directs resources away from the true social, environmental, and other drivers of unequal disease distribution [29].

Other researchers see race as a way station [19]. Many geneticists understand the category “race” is arbitrary, poorly defined, and inadequate, but see it as a means for understanding characteristics shared by many members of a group with common ancestry until advances in medical science make personalized medicine a reality [20].

In order to understand the causes associated with race that influence disease outcome, which are more environmental than genetic [14, 17, 29-31], researchers must actively search for them. In the meantime, using race in research can still be a powerful tool because it is associated with many of those environmental factors that influence health outcomes such as socioeconomic status, housing, education, employment, access to resources, diet, psychological stress, and cultural background [17, 20]. The problem with using the shorthand “race” to stand in for the many nonbiologic environmental contributors to health status is the problem mentioned earlier: all members of a designated “race” are not subject to those environmental pressures, while many from outside the “race” are.

Personalized medicine. The intention of personalized medicine is to treat the individual, but one can easily imagine how that intent can devolve into treating people based on the racial subgroups they are categorized as belonging to. Because not all patients respond in the same way to diseases and drugs, it would not be efficient to treat all patients with the newest, perhaps most expensive technology. A person with one variant gene of the two present at each locus along the DNA molecule may merely have a higher probability of response than members of the general population. To conserve resources and because genetic variation may be randomly correlated with membership in a “race,” personalized medicine may begin its scientific journey by using race as a predictor, but this, by definition, is not personalized medicine.

Conclusions

At this point, determining treatment response based on race and, thus, implying that race has deterministic genetic influence on health is misleading. One hopes clinicians apply findings such as McNearney’s with caution and that patients fully understand the implications of this research. It would be preferable if race were not used as a predictive marker in personalized medicine. Rather, the drivers of these hypothesized

racial differences such as coping or social support should be investigated and used instead as the predictive markers in personalized medicine.

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Timothy Chang is a MD-PhD student at the University of Wisconsin - Madison. His research focus is in translational biomedical informatics, particularly in prediction of disease, prognosis, and treatment response, which he hopes to apply to personalized medicine.

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STATE OF THE ART AND SCIENCE

Advances in Clinical Genomics

Aaron M. Lowe, PhD

The term “personalized medicine,” although vaguely defined, has become nearly ubiquitous in the past decade. The earliest known example of personalized medicine was the approach of Hippocrates, who in the fifth and fourth centuries BCE proposed that different medicines be used for different patients based upon their specific traits and symptoms. This philosophy is the basis for modern medicine, and in the past century it has experienced explosive growth along with the development and availability of new diagnostic tools.

Despite a continued dependence upon such diagnostic methods such as cell culture, immunoassays, and sophisticated imaging equipment, all of which provide information needed for individualized treatment, personalized medicine has evolved from basic science and is now closely identified with “-omic” approaches—genomics, proteomics, metabolomics, and so on. This article focuses on the state of genomics and its implications for the future. The chief difference between genetics and genomics is that genomics is the study of how the *molecular* composition of genes is responsible for production of specific proteins. Proteomics goes beyond genomics, aiming to discover correlations between protein expression and disease states at the cellular level.

Detection of genetic disorders on a molecular level will enable clinicians to characterize the cause of illness more rapidly, less expensively, and more precisely than traditional techniques such as immunoblotting. When combined, genetics, genomics, and proteomics are synergetic and promise enhanced (1) assessment of disease risk, (2) diagnosis, (3) prognosis, and (4) individualized drug treatment (pharmacogenomics).

In 2003, the Human Genome Project (HGP) published the first draft of the human genome at 99.99 percent accuracy. This monumental achievement took 13 years and cost \$3 billion. At present, the genome of an organism, humans included, can be sequenced in less than a week for several thousand dollars, with accuracy ranging from 92 to 99.99 percent, depending upon the method and technology. The cost and time of DNA sequencing has decreased exponentially over the past decade. The accuracy of sequencing technology will continue to improve, if for no other reason than that sequencing can be repeated until a sufficient level of statistical confidence is reached.

The steps in the sequencing method used in the HGP are time-consuming and costly. DNA must be purified, fragmented, cloned in bacteria to produce a sufficient quantity, purified again, used as a template to synthesize complementary chains of single-stranded DNA (ssDNA) that are separated by either capillary or gel electrophoresis, and imaged using fluorescent markers on the ssDNA. The resolution of separation is high enough that it is possible to distinguish ssDNA fragments based on a single nucleotide difference in length or a difference in the type of nucleotide in a single position within the fragment. In the chain termination (or Sanger sequencing) method used in the HGP, fluorescent markers (a different color for each type of nucleotide) are introduced onto the end of the ssDNA as the synthesis of each nucleotide is completed, allowing researchers to identify the gene sequence.

Emerging Genomic Technologies

Since the sequencing of the first human genome, innovations have significantly reduced the cost and time needed to sequence. First, the polymerase chain reaction (PCR) technique, which is less expensive and resource-intensive, has replaced bacterial cloning for culturing cells. Second, the physical size of the apparatus and, by extension, the volume of reagents necessary for sequencing are being miniaturized, making parallel sequencing and higher throughput possible, which has led to several commercially available tools. Instruments are now commercially available that operate on a scale smaller than a standard 96-well plate (so-called next-generation sequencers), with new companies already shrinking sequencing devices to the size of computer microchips (third-generation sequencers).

A third innovation is the development of more and faster methods of sequencing. Pyrosequencing, for example, allows investigators to dispense with the electrophoresis separation step required in Sanger sequencing. In pyrosequencing, the complementary ssDNA is sequenced as the chain grows because a momentary fluorescent signal is produced as each nucleotide is linked.

At the forefront of emerging detection technology are DNA microarrays [1]. Microarray technology uses predetermined sequences of ssDNA that have been immobilized on a surface. These immobilized ssDNA molecules serve as probes to capture small fragments of complementary DNA (approximately 100 base pairs) from solution. The probe DNA can be immobilized or directly synthesized in spots as small as roughly 100 square micrometers and in well-defined locations. This approach makes it possible to detect several thousand different sequences of DNA simultaneously from about 100 microliters of fluid.

As in Sanger sequencing, the captured DNA is typically labeled with a fluorescent marker for detection. Although the need to label DNA is a disadvantage, one advantage of DNA microarrays is that they simultaneously serve as both the initial purification step and detection step. Purification is an important consideration when the goal is to sequence DNA from one organism or to measure the amount of mutant DNA or foreign DNA (a virus, for instance) within a biopsy.

Other novel detection techniques are based upon numerous phenomena, such as changes in the optical, mechanical, or electrical properties of a substrate upon capture of a biomolecule or in the presence of byproducts of DNA synthesis [2-5]. These approaches do not require the use of fluorescent labels to detect captured biomolecules, thus simplifying and further reducing the cost of detection. Colorimetric tests based upon the use of metal nanoparticles can be used like human chorionic gonadotropin assays. In general, these techniques are designed to detect one or several distinct biomarkers, not to sequence entire sets of genes.

One third-generation technique is nanopore sequencing, which entails observing changes in electrical current as DNA passes across a nanometer-scale channel [2]. A variant of nanopore sequencing uses a similar concept, but the DNA is read by enzymatic cleavage of the base pairs as they pass through the pore, one at a time.

Limitations

Regardless of the cost and accuracy of next-generation and emerging detection techniques, the purpose of genome sequencing is to identify specific mutations; otherwise 100 percent accuracy in sequencing is meaningless. Interestingly, one major conclusion of the Human Genome Project was that 99.9 percent of DNA base pairs are identical from one individual to another. Does this mean that for genomics to be a clinically useful tool for personalized medicine far greater accuracy is needed to determine more subtle genetic differences that are associated with disease states? Because there are 3 billion base pairs of DNA in a human cell, achieving 99.99 percent accuracy in sequencing means 300,000 possibly different, disease-causing base pairs can escape detection. Frequently, even a single nucleotide polymorphism (SNP) can be the source of a genetic disorder. This is why, for clinical testing, the most common approach is to simply sequence a small panel of genes to search for a specific disease. These tests typically cost \$1,000 or more.

Belief in the ability of genomics to assess the risk of or diagnose disease depends entirely on the assumption that disease states originate from mutations in an individual's genome. However, complications in this path toward risk assessment are introduced by (1) the need to first associate mutations or so-called biomarkers with known disease states, (2) the ability or inability to detect these biomarkers in individuals, and (3) the fact that disease states are often caused by interactions among many genes in addition to environmental factors.

Although numerous potential biomarkers for disease have been identified in the scientific literature [6], the need to identify biomarkers for more diseases is still the primary obstacle to overall progress in genomics as a basis for personalized medicine. Moreover, it is not at all certain that meaningful risk assessment for individuals is possible for most genetic diseases. While there are certain heritable mutations that can predict the risk of disease with high certainty, as is the case with Huntington disease and cystic fibrosis, predictions of other diseases are more complex and can only be made with a low level of confidence (26 percent, in the case of lung cancer) [7]. Finally, although targeted therapy based upon individual

genetics is achievable, the co-development of diagnostics and therapeutic agents is constrained by cost, which can exceed \$1 billion.

Legal Concerns

Several legal obstacles hinder the use and development of genetic screening. As described above, the identification of biomarkers is a key element in the development of disease assays. The discovery of biomarkers is resource-intensive, and the intellectual property (IP) related to their discovery is guarded in the private sector by patents to ensure the recovery of costs incurred in the process. In fact, a staggering 20 percent of genes identified in the HGP has been referenced in patents [8]. As a result of these numerous patents, sometimes referred to as patent “thickets,” multiplexed assays such as DNA microarrays are subject to so many licensing fees that their development becomes impractical—a significant loss to society.

The growing demand for genetic screening has also led to questions of reliability. Direct-to-consumer test kits have been met with apprehension because of possible misuse and misinterpretation of results by people who have not consulted a physician. It is important to keep in mind that interpretation of prescription tests is generally not easy for physicians without the consultation of an expert such as a genetic counselor. Examples of FDA-approved prescription tests include assays for an enzyme (MHFTR) implicated in diseases related to thrombosis and coronary artery disease and a gene mutation (CFTR) responsible for cystic fibrosis in newborns. Because of the complexity of test interpretation and the variation in scientific literacy across society, it is inevitable that misinterpretation of test results, particularly from direct-to-consumer home tests, will result in self-directed actions such as changes in behavior or usage of medications.

Conclusions

Genetic screening and personalized medicine are still in the early stages of development and the approach taken at present can still have significant implications for the future. In the long term, the integration of genetic screening into standard medical care will be determined by demand. Demand as a driving force has pros and cons. As demand increases, more biomarkers will be identified, but research into less common “niche” diseases will likely be neglected (as they often are in drug research) and “patent wars” may cause a bottleneck in innovation. due to the cost of development and the low return on investment. But if physicians and patients create a demand, then genomics-based personalized medicine can become standard practice.

The cost of genetic screening for individual patients is prohibitive at present, but this may change. It is conceivable that medical insurance companies may see the benefit of early risk assessment and disease detection and begin to cover genetic screening, which may help patients by allowing early treatment or prevention of genetic diseases. How effective this type of personalized medicine will be, given the complexity it introduces, is still unknown.

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Aaron M. Lowe, PhD, completed his doctoral studies in the laboratory of Nicholas L. Abbott, PhD, and Paul J. Bertics, PhD, with a focus on the detection of biomolecules through novel techniques.

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HEALTH LAW

Genetic Diseases and the Duty to Disclose

Shawneequa Callier, JD, MA, and Rachel Simpson

Amy, a long-term patient of yours, has been diagnosed with a bipolar disorder that has a hereditary component likely to manifest itself in some of her relatives. While efforts to identify specific susceptibility genes are still underway, disclosure of her test results to siblings and children, followed by careful monitoring, could improve the future health of her family. Worried about the possibility of estrangement, however, Amy says that she is unwilling to warn her at-risk relatives of the genetic link to bipolar disorder that they may share. As a clinician, what are your duties to Amy and her family, and how are they affected by patient confidentiality requirements?

With increased use of personalized genomic medicine (PGM)—individualized care that incorporates patients’ genetic profiles for treatment and diagnosis purposes—scenarios like the one described will be more common [1]. Using genetics to diagnose and treat medical conditions raises significant privacy and genetic discrimination concerns because diagnoses of gene-related health conditions may have implications for those related to the patient. The law, however, has been inconsistent in its guidance to physicians regarding their duties to nonpatient family members, especially when the implications of patients’ genetic test results are unclear.

Generally, physicians only have duties to their patients, and, unless a patient expressly consents to disclosure or a law requires it, they are obliged to hold patients’ medical information in the strictest confidence [2]. This professional obligation is intended to encourage patients to communicate fully and candidly with their doctors [3]. If they can trust that their communications will remain confidential, the argument goes, patients will be more forthcoming about behaviors and history that might influence treatment strategies [3]. Exceptions to confidentiality exist, primarily to prevent a contagious threat to the public’s health from communicable disease [3], to prevent foreseeable, serious risk to an identifiable victim [3], and when violence or abuse is the suspected cause of a patient’s injury. The Health Insurance Portability and Accountability Act requires potential danger or imminent threat for disclosure of medical information to third parties [4].

With personalized genomic medicine, the threat to family members is rarely imminent and the level of foreseeable harm is often difficult to predict. Further, PGM complicates what it means to act in the best interest of the patient. Variations in family dynamics, for instance, can quickly and dramatically transform the

fulfillment of professional duty in one situation to a questionable act in another. Unlike traditional medical test results, genetic test results often provide only probabilistic information rather than a clear diagnosis or definite prediction of disease. Whether relatives should be warned of hereditary conditions when there are no means of prevention, treatment, or cure is unclear, and there is little support for warning underage family members of adult-onset conditions [5]. Further, patients' relatives have a "right *not* to know" about their genetic makeup, so informing them might interfere with their autonomy, in addition to breaching the patient's confidentiality [6].

Case Law

In considering physicians' duty to warn at-risk family members of possible harm from genetic variations, the courts provide limited and conflicting guidance.

In a 1995 case, *Pate v. Threlkel*, the plaintiff, Mrs. Pate, inherited medullary thyroid carcinoma from her mother and sued her mother's physician for negligent failure to warn the mother that her children might inherit the cancer risk [7]. Mrs. Pate alleged that the physician "knew or should have known" of the risk to his patient's children and had an affirmative duty to recommend immediate testing for the patient's children. Had she been warned, Mrs. Pate argued, she would have sought preventive treatment for the disease at an early stage in its development. The court ruled in favor of the physician that "in any circumstances in which the physician has a duty to warn of a genetically transferable disease, that duty will be satisfied by warning the patient" [7]. In this instance, the court did not impose a duty upon the doctor to warn a third party, but merely to encourage the patient to warn her at-risk relatives.

One year later (1996), a New Jersey appellate court came to a different decision. In *Safer v. Estate of Pack*, the plaintiff's father had died of multiple polyposis, an inherited condition that can develop into cancer if it is left untreated [8]. Because the plaintiff, Mrs. Safer, was a child when her father died, she only learned of her predisposition to developing the disease when she was diagnosed with multiple polyposis herself in adulthood. The plaintiff sued her father's physician, alleging a duty on the part of the doctor to warn at-risk relatives of the possibility that they might develop this treatable condition. The *Safer* court ruled that "the duty to warn might not be satisfied in all cases by informing the patient." Sometimes, the decision went on to say, the physician might have to resolve the "broader duty to warn and...fidelity to the expressed preference of the patient that nothing be said to family members" about the disease [8]. These holdings and case law in general are inadequate to apply to the gamut of scenarios in which physicians could apply PGM routinely.

Returning to Amy's condition, we have little knowledge about her relatives' interest in or understanding of genetics. With a specific genetic susceptibility test still in development, warning Amy's relatives could potentially *cause* "avoidable harm," especially if the clinician is ill-equipped to properly advise the family. Encouraging Amy to inform her at-risk relatives that she has an inherited bipolar disorder (as

urged in the *Pate* decision) may be appropriate, but creative and practical solutions for the family may be needed, such as directing them to resources and people who can explain the health, emotional, and discrimination risks for those who may wish to seek confirmatory testing.

An Ethical Approach

While some scholars have called for the adoption of a system in which genetic information is shared among family members by default, others prefer to quantify the levels of genetic risk and probability of harm on a case-by-case basis [1]. Until legal agreement is achieved on when and how to make sensitive disclosures to at-risk family members, clinicians can at least fulfill their duty to fully educate their patients about the meaning and scope of their diagnosis [9].

For instance, patients should understand that guidelines on the duty to inform at-risk relatives of possible genetic conditions differs among professional organizations. For potentially life-threatening genetic mutations, the Institute of Medicine recommends disclosure when the following conditions are met: (1) irreversible or fatal harm of the relative is highly likely, (2) attempts to elicit voluntary disclosure fail, (3) disclosure will prevent harm, (4) the harm resulting from the disclosure is less than the harm that may result from failure to disclose, and (5) there is no other way to avert the harm [10]. In such cases, the disclosure should be limited to the information necessary for diagnosis or treatment of the relative [10]. In nonfatal cases, a clinician's duty may be fulfilled by encouraging patients to communicate with relatives [11] or providing the name of a counselor who specializes in such discussions. The *AMA Code of Medical Ethics*, however, does not construe finding and notifying family members as a physician's duty, though it does recommend that physicians inform patients in advance of what they expect them to disclose to their families and be available to assist in this communication [9].

Conclusion

Medical care tailored to the genomic makeup of an individual can reduce adverse drug reactions, improve the efficacy of treatment, and help patients better comprehend gene-environment reactions that influence individual health. Because an important genetic mutation can affect family members, however, concerns about confidentiality are likely to increase as personalized medicine becomes a more widely used tool in clinical management, and clinicians' duties may widen to include at-risk family members. Medical staff should be conscientious about their patients' potential needs for genetic counseling (given by the clinician or a qualified genetic counselor) and be ready to advise patients on communicating their diagnoses to family members.

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Shawneequa Callier, JD, MA, is an assistant professor in the Department of Clinical Research and Leadership at the George Washington University School of Medicine and Health Sciences in Washington, D.C.

Rachel Simpson is a graduate student pursuing a master of public health degree in epidemiology at the George Washington University School of Public Health and Health Sciences in Washington, D.C. She received a bachelor of science degree in cognitive science with a specialization in neuroscience from the University of California, San Diego.

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POLICY FORUM

Regulation and the Fate of Personalized Medicine?

Dov Greenbaum, JD, PhD

Personalized medicine can be succinctly described as the right dose of the right drug for the right indication for the right patient at the right time [1], the antithesis of the former blockbuster one-drug-fits-all approach. With more than 70 drugs that may be classified as “personalized” already on the market [2], this new paradigm in drug development may become a real force in the biopharmaceutical industry. That industry is eager to exit a particularly difficult innovation slump that also coincides with a “patent cliff,” i.e., the expiration of many patents for blockbuster drugs that heretofore limited generic competition in exceedingly lucrative markets [3].

The current bleak economic forecast for biopharm notwithstanding, there are powerful incentives drawing drug companies into this new method of drug development. Personalized medicine promises to increase efficacy in subpopulations of patients, providing opportunities to revive defunct or failed drugs with new, narrower indications and minimizing adverse drug reactions among those for whom the drug is no longer indicated.

A recent example of a personalized medicine drug passing FDA standards is Perjeta, approved for use in combination with Herceptin (itself a personalized treatment specifically approved for use on patients with overactive HER2 receptors) and docetaxel chemotherapy to create a comprehensive blockade of human-epidermal growth factor receptor (HER) signaling pathways for the treatment of HER2-positive metastatic breast cancer. Patients are required to take a genetic test to determine whether their cancer is HER2 positive before they can be prescribed the drug [4].

The concept of personalized medicine isn't novel; orphan drugs, those medicines with very narrow labeling that encompass only a sliver of the population, are in essence a form of personalized medicine, but without all the fancy recent “-omics” innovation driving current efforts in that direction.

This current incarnation of personalized medicine, however, may perhaps be best thought of as a third attempt to monetize the successful sequencing of the human genome. The first attempt entailed finding drug targets within what was largely an unannotated sequence of genetic code. The second, ongoing effort, still too young to evaluate [5], proposes using genome-wide association studies (GWAS) to investigate genetic sources of complex and often chronic diseases, or in some cases to suggest alternative or more specific uses of a drug [6]. The third, present effort aims to provide precise diagnoses and highly directed treatments based on genetic data [7].

This third wave comes as we are experiencing a precipitous drop in the price of both genetic sequencing and computing power and memory that has led to the nascent personalized genomics industry. This industry provides genetic data to the public relatively inexpensively. A phenomenal accomplishment: compare the current forecast of whole genome sequencing for \$1,000 or less with the \$3 billion price tag on the Human Genome Project completed in 2003 [8, 9].

Since personalized medicine often (but not always [10]) relies on knowledge of a particular genetic variant in a patient, it would be of great benefit if a large percentage of the public had easy access to their genomic make-ups, which could then be matched against a growing library of single nucleotide polymorphisms (SNPs), copy number variations (CNVs), other biomarkers, and proteomic, metabolomic, or epigenetic data associated with disease, drug metabolism, and other relevant indicators. Despite the exciting possibilities of personalized medicine, there remain substantial regulatory, legal, and social hurdles.

Regulation and the FDA

Many of the hurdles have to do with the Food and Drug Administration (FDA). While the FDA has indicated that it is interested in revising the regulatory structure to promote personalized medicine, the current regulatory uncertainties are likely to be a drag on financial investment in the field.

Changes will require up-to-date expertise in broad swaths of science and will necessitate significant shifts in the way the FDA does business—unprecedented cooperation across multiple centers and departments with different cultures, regulations, legal concerns, and foci. For example, personalized medicine often requires the integration of drugs and diagnostics, which are currently handled by least two separate FDA programs with different standards. This may cause logistical trouble. A given drug and its diagnostic companion may be produced by different corporations that would need to coordinate their distinct needs across multiple agencies and subfiefdoms within the FDA. Whether that means governing them by similar regulations, putting them through similar evaluation processes, or just reviewing the very different technologies at the same time remains to be seen.

Whereas previously a drug and its indications may have been thoroughly understood by a particular set of experts at the FDA, personalized medicine labeling may require several experts in nonoverlapping fields to develop a shared knowledge base. Similarly, the FDA will need to build additional capacity to define the optimal subpopulation for a particular drug, which is likely to require cooperation between a mix of clinical and research scientists. This cooperation is of particular importance since regulators are likely to overestimate the precision of genomic data when simpler biomarkers may be more efficient and more medically relevant.

Further, clinical trials will use smaller populations determined by relevant biomarkers in the clinical analysis of the drug, rather than being conducted in the

more random fashion of the past, when populations for trials were not determined by genomic information [11]. This, and the changing conception about the ethical usage of controls in trials where data strongly suggests that the drug will work with few adverse reactions, may change the way drug trials are conducted and evaluated. And, given the sometimes-controversial use of retrospective analysis (in which researchers, lacking genomic data on a new treatment, rely on, for example, data on race instead), the FDA will need to work toward better policing these analyses [12].

This is not to say that the FDA hasn't been trying [13]. In 2003, the FDA established the Voluntary Exploratory Data Submissions (VXDS) program, a repository for genetic data that the biopharmaceutical industry was keeping on its products [14]. Drug companies, however, were wary of submitting additional data that could potentially harm their applications for approval, and it took a number of years before they actually started providing the data, which will help the FDA, among other things, understand whether genomic data should be included in drug labels.

In 2011, the FDA issued a number of drafts for guidance that have implications for the regulation of personalized medicine [15-18]. These drafts typically deal with diagnostic tools and devices that may be necessary when determining whether a particular patient has a particular biomarker, for example, when developing drugs that can only be used with companion diagnostic tests. Some of the relevant parties felt that the FDA guidance actually indicated that the FDA did not yet have a good grasp on the nature of the personalized medicine industry, and particularly on how to promote innovation and investment [19].

FDA commissioner Margaret Hamburg has also voiced support for new science and innovation in general and personalized medicine and pharmacogenomics in particular [20, 21]. Further, earlier this year, Congress passed and the president signed FDA user-fee legislation that included provisions to develop the agency's capacity to review data on biomarkers and pharmacogenomics [22]. This apparent signal of confidence by Congress and the FDA as to the importance of the personalized medicine industry may provide additional confidence to the industry in the regulatory system that polices it.

The onus of revamping the regulatory climate is not borne by the FDA alone. Regulatory control of many diagnostic tests, including genetic tests, involves both the Clinical Laboratory Improvement Amendments (CLIA) program administered by the Centers for Medicare and Medicaid Services of the Department of Health and Human Services and the FDA's Office of In Vitro Diagnostics. CLIA typically regulates the technical accuracy of the test and the FDA typically regulates the test's medical applications.

Financial Incentives

In addition, regulatory and legal decisions may inhibit or discourage innovation. For example, it's unclear how recent efforts in reforming national health care [23] will affect the reimbursement process for diagnostic testing and other aspects of

personalized medicine. It's thought that payors who need evidence of the effectiveness and financial viability of a treatment will be able to obtain that data from, for example, the nongovernmental Patient-Centered Outcomes Research Institute (PCORI) established by health care reform. But cost-cutting measures created by the same reforms may prevent them from being able to do so [24, 25]. Contrast, for example, the position of Gregory Conko's and Henry I. Miller's *Forbes* editorial claiming that "ObamaCare threatens personalized medicine" [26] with law firm Foley and Lardner LLP's assessment that "the bill offers support for personalized medicine" [27].

Further, in the recent Supreme Court case *Mayo v. Prometheus* [28] the court reversed an appellate decision of the Federal Circuit by finding that specific patent claims that included a widely used method for titrating and optimizing the dosage of a drug were invalid. The court ruling, criticized by many for conflating basic concepts in patent law [29] but now nevertheless being followed in lower courts [30], deemed the method was unpatentable. The court, it appears, feared that patenting such tests might "interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research" [31].

However, given that the United States Patent Office has only just released their guidelines in light of the Supreme Court decision [32], it's unclear whether the end result will be the promotion of innovation, as anticipated by the courts, or more likely a chilling effect on the development and use of personalized-medicine diagnostic tests that rely on the protection of intellectual property to obtain funding from wary investors.

Furthermore, personalized medicine's tendency to move away from the one-size-fits-all blockbuster model for pharmaceuticals will result in a new drug paradigm involving substantially smaller markets with correspondingly smaller incentives for drug innovation and the likelihood that drug companies might invest in me-too drugs or generics [33].

The standard drugs for Alzheimer disease, cancers, asthma, and other chronic diseases can be ineffective on between a third and three-quarters of patients taking them [34]; many widely used drugs are ineffective for large swaths of the population. The ethics of selling those drugs notwithstanding, personalized medicine will effectively destroy the profits of that business model.

Regulations will also need to be updated to prevent pharmaceutical companies from abusing the Orphan Drug Act [35], which was enacted to promote pharmaceutical research for the portion of the population with rarer diseases that may be disenfranchised from drug development by the pharmaceutical industry. Such abuse might entail applying for funding that belongs to drugs for rare conditions, and salami slicing a broad target population into more specific populations to repurpose the drug as several drugs efficacious for smaller populations [36].

Conclusions

This list is not exhaustive; many legal, regulatory, social, and ethical obstacles to the development of a personalized genomic drug industry remain. For example, social concerns may be a sticking point. Thus, despite the efforts in developing the Genetic Information Non-Discrimination Act (GINA) [37], reasons remain for people to be wary of releasing their genetic data, including, but not limited to, the obvious loopholes that the act contains for providers of long-term care, disability insurance, and life insurance. New privacy regulations need to be in place before much of the population will be comfortable releasing genetic and genomic data, particularly to their insurance companies. The future of this promising nascent technology will be in large part determined by regulatory and legal changes.

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Dov Greenbaum, JD, PhD, is an assistant (adjunct) professor of molecular biophysics and biochemistry at Yale University in New Haven, Connecticut, a nonresident fellow at the Center for Law and the Biosciences at Stanford University Law School in Palo Alto, California, and an attorney at Pearl Cohen Zedek Latzer in Israel.

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POLICY FORUM

Certificates of Confidentiality and the Marshfield Clinic's Personalized Medicine Research Project

Wendy Foth, Carol Waudby, and Murray H. Brilliant, PhD

Enrollment in research studies is often limited by the fear that one's personal information cannot be kept private. One way researchers can address this is by obtaining a certificate of confidentiality (CoC) for their study. This article briefly reviews what a certificate of confidentiality is, how to obtain one, and the Marshfield Clinic's experience in recruiting for the Personalized Medicine Research Project.

Protecting the privacy and confidentiality of participants is paramount in the recruitment for research studies. In developing research protocols, therefore, efforts to protect the information that participants will disclose need to be thoroughly planned, implemented, and communicated to participants. A certificate of confidentiality is one of the resources available for maintaining privacy and confidentiality [1].

Issued by certain Department of Health and Human Services (DHHS) agencies, a CoC allows researchers to "refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level" [2]. This additional level of protection helps researchers maintain participants' privacy and confidentiality and promotes enrollment in the research study by reassuring participants.

A study qualifies for a CoC if:

1. This study will collect sensitive personally identifiable information; and/or
2. This study will maintain consent forms with identifiable information other than names (e.g., social security numbers, addresses, etc.).
3. This study cannot be conducted anonymously—that is, the research itself relies on personally identifiable data to gather data.
4. The study subject matter falls within the research mission of the NIH and its Institutes, Centers, and Offices.
5. Data is maintained within the United States [3].

Once a CoC has been obtained, the study subjects must be informed of its existence, protections, and limitations. The institution obtaining the CoC must also submit an amendment application 3 months in advance of making any significant changes in personnel who have a major role in conducting the study, the aim of the study, or drugs being administered.

Marshfield Clinic's Personalized Medicine Research Project

The Personalized Medicine Research Project (PMRP) is studying a large cohort of residents of Central and Northern Wisconsin [4]. This database, which contains genetic, medical, and environmental information, is maintained by the Marshfield Clinic Research Foundation [5]. The main goals of the project are to better understand the roles of genetics, environment, and behavior in the development of disease and response to medications and how to use this information to enhance personalized patient care. The power of the associations among genetics, phenotypes, and the environment goes up as enrollment in the study increases because results yield a more accurate representation of the population. To boost enrollment, the PMRP applied for, and received, a CoC.

At an enrolling appointment, information about participation is thoroughly reviewed with the potential participant by a person or at a computer kiosk [6]. Our current informed consent processes and the frequently asked questions page on our web site include this (or similar) language about the CoC:

To help us protect your privacy, we have obtained a certificate of confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding [7].

Government involvement may or may not promote participation; some prospective participants have confidence in the government involvement, some are neutral, and some distrust it. Some people choose not to participate due to privacy concerns, especially related to insurance, and no security measure will be enough to outweigh those concerns. This is understandable, as there is never a total guarantee of protection under any security system.

Ultimately, the level of trust and confidence a person has in the facility or institution conducting the research is the main determinant of his or her participation. This is why it is necessary to explain what measures are in place to protect privacy and confidentiality. Having layers of protection—internal, external, and governmental—is a way of showing how seriously researchers take maintaining the security of participants' information.

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Wendy Foth is a research coordinator with the Center for Human Genetics at the Marshfield Clinic Research Foundation in Marshfield, Wisconsin.

Carol Waudby is a research coordinator with the Center for Human Genetics at the Marshfield Clinic Research Foundation in Marshfield, Wisconsin.

Murray H. Brilliant, PhD, is the director of the Center for Human Genetics at the Marshfield Clinic Research Foundation and the principal investigator for the Personalized Medicine Research Project in Marshfield, Wisconsin. Dr. Brilliant conducts research on complex human genetic disorders.

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MEDICINE AND SOCIETY

Will Personalized Medicine Challenge or Reify Categories of Race and Ethnicity?

Ramya Rajagopalan, PhD, and Joan H. Fujimura, PhD

In the last 5 years, medical geneticists have been conducting studies to examine possible links between DNA and disease on an unprecedented scale, using newly developed DNA genotyping and sequencing technologies to quickly search the genome. These techniques have also allowed researchers interested in human genetic variation to begin to catalogue the range of genetic similarities and differences that exist across individuals from around the world, through initiatives such as the International Haplotype Mapping Project [1]. These studies of human genetic variation promise to produce new kinds of information about our DNA, but they have also raised ethical questions.

Early results from genome-wide studies of possible links between DNA and various medical conditions are being used by various actors to develop what they call “personalized medicine,” the effort to tailor and individualize diagnoses and treatments for use during routine medical care. The promises of personalized medicine are built on the idea that each individual’s genome is unique. They are also built on the idea that genetic variation among individuals will help explain differential susceptibilities to disease and why some patients respond better to some treatments than others. To this end, researchers have focused on characterizing genetic differences between individuals and groups.

Researchers refer to the genomic sites where these genetic differences occur as SNPs (single nucleotide polymorphisms) and CNVs (copy number variations). These “genetic markers” of human variation are thought to comprise only a tiny proportion, around 0.5 percent, of the roughly 3 billion bases that make up a human genome [2]. Still, many medical genetics researchers are exploring these differences, which they argue may be medically relevant. By genotyping or sequencing the genomes of thousands (and in some cases hundreds of thousands) of individuals, genetics researchers have generated several tools that are being used to dissect the possible contributions of differences in DNA to common diseases. They are also investigating links between genetic variation and differences in patients’ responses to drugs or other medical treatments, a set of practices which has given rise to the field of pharmacogenomics.

As noted above, the basic premise of efforts to develop personalized medicine is that each individual is genetically unique. However, many individuals may have some genetic markers in common, such as a particular genetic variant that might be related

to a particular disease. In order to make statistically meaningful assessments, researchers document how often they have observed a particular genetic variant in a particular group of people. One challenge they continue to face is how to select and delineate these particular groups of people, and how to report these genetic “frequencies” in ways that might be meaningful for medical purposes.

Proponents of personalized medicine argue that bringing this new set of practices to the clinic for medical diagnosis and treatment will revolutionize the delivery of health care. But in their efforts to link genetic differences to disease, some researchers claim they can also distinguish other kinds of differences in DNA among people that may or may not be health-related. They argue that these other differences are attributable to membership in different groups defined by race [3, 4] or continental ancestry [5]. These researchers argue that such genetic patterns may have medical importance.

We note two ethical dilemmas posed by the claims made by these and other similar studies that attempt to link genetics, ancestry, and disease, particularly when ancestries are described in terms of continent of origin, for example, European, African, and Asian. Such labels are based on socioculturally defined U.S. categories of race and ethnicity, such as white, black, and Asian. The first dilemma arises because these studies are based on a relatively small subset of individuals who identify within any of these continental ancestry or race groupings. Thus, any extension of study findings to others who identify within these broad groupings would be fraught with problems of accuracy and precision. Indeed, much genetic evidence suggests that those who identify with a particular U.S. race or ethnicity census category are quite genetically heterogeneous [6]. Thus, there is no neat correspondence between genetic variation and one’s assumed race or ethnicity. Indeed, no single pattern of genetic variation is diagnostic of affiliation with any particular race or ethnicity [7].

Second, and consequently, many worry that the new technologies being used to develop personalized medicine may also become technologies that are used to define “genetic signatures” for, or “genetic stereotyping” of, different racial or ethnic groups. This aspect of personalized medicine, if developed and nurtured into broader clinical use, will popularize the idea that it is possible to infer underlying genetic makeup from an observer-defined or self-reported race or ethnicity, when even proponents of using race in genetics research argue that this is a logical fallacy [5]. This possibility recalls some of the past attempts to link race and biology, e.g., the eugenics movements of the early twentieth century.

Indeed, race is not new to medical decision making in the U.S. For decades, it has been common practice among American medical clinicians to use race as one factor among many when deciding among possible diagnoses and treatments. There is a long-standing view in medicine that certain diseases travel more frequently in certain racial groups and a belief that certain groups may respond better (or worse) to certain treatments than others. However, epidemiological evidence of racial differences in

disease incidence is not evidence of race-specific genetic susceptibility to disease. Many studies have shown that sociocultural factors that differ by social race categories, including socioeconomic status, contribute significantly to racial differences in disease incidence [8].

Nor is race new to American medical genetics. Many scholars have analyzed the American eugenics movements of the early twentieth century and the more ethically aware field of medical genetics that they eventually gave rise to in the mid-twentieth century [9, 10]. Prior to the start of the Human Genome Project, medical genetics focused primarily on relatively rare, familially inherited diseases. Certain generalizations about the relationships between race and genetics, now part of popular understanding and medical training programs, grew out of these studies. For example, medical school and college biology curricula continue to propagate the idea that some single-gene, highly heritable diseases, like Tay-Sachs disease or sickle-cell anemia, are prevalent in only certain groups—as in Jewish and African American groups, respectively—than other groups. What is often not acknowledged is that Tay-Sachs has also been observed at high prevalence in non-Jewish groups in Quebec, Canada [11] and that sickle-cell and other hemoglobin disorders are common in many groups around the world [12]. The misconception that a particular disease like sickle-cell is specific to African Americans may lead to patients being misdiagnosed or diagnosed too late in the progression of disease simply because they are not of the ethnic group “marked” by the disease.

Just as there are ample counterexamples to these and other generalizations about race and single-gene diseases, so too is the evidence growing against easy links between race and DNA when it comes to the common and complex diseases of current interest in medical genetics. Contemporary medical genetics is using the latest genotyping and whole-genome sequencing tools to explore conditions prevalent in the general population, such as diabetes, heart disease, and asthma, which are not considered to be familial diseases, though they exhibit some heritability. The occurrence of these diseases has long been suspected to be closely tied to one’s environment—factors such as diet, exercise, smoking and drinking habits, air and water quality, standard of living, and so on. Differences in these environmental factors may contribute to differences in disease incidence among different race and ethnic groups, owing not to genetic predispositions but to correlations with socioeconomic disparities that exist between different race and ethnic groups in the U.S. [8].

Indeed, genome-wide studies have not yet been able to find associations between DNA variations and these diseases that are strong enough to explain their apparent heritability [13]. This may provide genetic evidence for previous epidemiological views that these diseases have a high environmental component (which may be “heritable” in its own way through generational inheritance of socioeconomic conditions) and perhaps only a very small genetic component. Finally, to compound matters, recent findings in medical genetics strongly suggest that any genetic contributions to complex diseases have an underlying biology that is much more

complicated than can be measured or indicated by the mere presence or absence of genetic markers.

As DNA genotyping and sequencing technologies become faster and cheaper, many actors and institutions are playing prominent roles in efforts to apply these technologies during routine clinical care. The question that remains is, will these new genomics technologies be used to support the idea that differences among individuals, when grouped along racial or ethnic categories, are medically relevant? Many geneticists have shown that categories of race, ethnicity, or “population” as proxies for genetic variation are inaccurate tools for assessing disease risk in medical settings [6]. Similarly, using genetic patterns as readouts of one’s “real” ethnicity or race makes no sense when racial and ethnic groups are social categories constructed within specific historical and cultural situations and not based on genetics. In the U.S., those who identify with any particular census race or ethnic category are far from genetically homogenous, which is not surprising since affiliation in such groups is driven by sociocultural influences. Methods now exist whereby genetic variation may be interrogated at the level of individuals. Why use these methods to redraw lines between racial groups, especially since race groups are not genetic groups, and then use these groups to organize “personalized medicine”? This defeats the aim of personalized medicine, which is to tailor treatment so it is more effective for each individual’s specific combination of health factors.

To return to our first point, many researchers argue that race is a poor proxy for understanding the distribution of human genetic variation. They also argue that genetic variation is not distributed by race, especially not by race defined as continental ancestry. Indeed, most genetic variation occurs within any such groupings rather than between them [6]. However, several direct-to-consumer genetic testing companies sell services that claim to be able to analyze an individual’s DNA and quantify the percentage of their ancestry from each continent and in some cases from regional or tribal groups in Africa.

There are problems with the ways that direct-to-consumer testing companies define continental ancestries. They first select a small subset of present-day individuals whom they judge to be representative of each continent or geographic area, and use the genomes of these people as the reference point for determining which test samples have ancestry from that particular area or tribe [14, 7]. As many commentators have observed, population groups are not and historically have not been discrete, bounded entities, and the definitions used by researchers are neither standardized nor straightforward [15]. Finally, the vast majority of human genetic variation remains unrepresented in genomic databases today—the sample sizes in the databases are exceedingly small and limited to a few individuals who have donated DNA. These databases are too small to build generalizations about different kinds of human groups and their relationship to genetics and disease.

Parsing disease susceptibilities by continental ancestry or race groups and linking these susceptibilities to genetics in medical decision making may have negative

consequences for individual health and well-being. For example, the use of race as a proxy for underlying genetic variation could result in misdiagnosis or incorrect treatments for patients assumed to be part of the group(s) with genetic predisposition to the disease in question. Such generalizations may also be detrimental to groups not directly implicated. For example, associations between specific diseases or genetic signatures and particular groups may result in a higher chance that the correct diagnosis of the disease in question will not be made for patients assumed not to be part of these groups.

In addition, many argue that a focus on trying to find genetic differences between race and ethnic groups, in order to explain differences in disease incidence, will distract needed attention and scarce resources away from other more significant factors leading to differential disease susceptibilities among sociocultural groupings, such as quality of life and standard of living, socioeconomic status, neighborhood, and access to health and education.

For these reasons, many medical professionals and scholars are worried about the implications of the use and misuse of race in the new clinical pathways being pursued by advocates of personalized medicine. As many have argued, using race as a lens through which to determine treatment decisions could (and has) opened the door to instances of misdiagnosis or incorrect treatments for individuals [16]. If race becomes the organizing variable for genetic variation, the potentially democratizing new tools of personalized medicine could become instead the instruments of a new means of stereotyping groups of people, legitimized by the perceived authority of genetics.

Personalized medicine is at a crossroads. It may be used to sustain old beliefs about racial differences, yoking them to supposed differences in health and susceptibilities to illness. This in turn may fuel the view that our genetics establishes an innate, definitive roadmap of our future health. However, recent studies of hundreds of common complex diseases suggest that genetics has only a small part to do with our susceptibilities to these diseases.

An alternative route for personalized medicine is for its practitioners to take stock of the various environmental onslaughts that individuals are subjected to and tailor medical diagnoses and treatments by considering each patient's unique complement of environmental and biological factors that may contribute to health or disease. If personalized medicine is to bear out its name and become truly "personalized," then a focus on racial differences at the level of the genome constitutes a step off the path with many ramifications, including the possibility of racial and ethnic stereotyping and discrimination during routine medical care that could lead to misdiagnoses and ineffective treatment regimens. Efforts to achieve personalized medicine in clinical settings would do better to focus on patterns in genomes and how such patterns may be associated with disease, rather than trying to find genetic correlates for existing racial and ethnic categories.

Given that the genomics of disease is still in its infancy, the medical relevance of genomics findings remains uncertain. Genomics researchers have a responsibility to be aware of the ways in which they draw boundaries around groups based on genetics, and to communicate the caveats associated with their findings to various publics, other health researchers, medical practitioners, and clinicians. In the push for personalized medicine, such information will be vital in preventing new waves of genetic determinism or new practices of “genetic stereotyping” around disease and race.

Doctors and medical decision makers must also be cognizant of the limitations and caveats associated with findings from genomics studies. Reliable and accurate application of findings from genomics research, particularly when extended to individual patient care, remains for the most part an elusive enterprise, fraught with uncertainty. With regard to decisions relevant to a patient’s health and well-being, the knowledge emerging from genomics is still a long way from being able to reliably inform practitioners about the most effective therapy, treatment or course of action.

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Ramya Rajagopalan, PhD, is a postdoctoral research fellow in the Department of Sociology at the University of Wisconsin - Madison and an ethics fellow at the Morgridge Institute for Research. Dr. Rajagopalan (with Joan H. Fujimura, PhD) studies the social, ethical, and clinical impacts of genetics, biomedicine, and biotechnology.

Joan H. Fujimura, PhD, is a professor of sociology and professor of science and technology studies in the Robert F. and Jean E. Holtz Center at the University of Wisconsin - Madison. Dr. Fujimura studies the social and ethical aspects of genetics, molecular biology, biotechnology, and biomedicine. Her research has been supported by NIH's National Human Genome Research Institute, the National Science Foundation, and the University of Wisconsin Graduate School.

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IMAGES OF HEALING AND LEARNING

Ghazal of Algorithms

Sara Wainscott, MFA

Editor's note: The ghazal, a mainly Middle Eastern poetic form that dates back to the seventh century, traditionally takes up metaphysical questions and evokes longing, love, and loss. It is made up of couplets distinct from each other in theme, tone, and imagery but joined together in their second lines, which end with a rhyme followed by a refrain. The final couplet often references the author, sometimes by name [1].

We're alive down here no matter what the topography tells.
Pixels, dewdrops, grains of sand, microscopography of cells.

Scientists categorize chemical pairs, sequencing our genome.
The ark carried pelicans, their bones carried ink—calligraphy of cells.

I'm sorry for the things I say to hurt you, the things I never say.
We're still evolving, each revising our autobiography of cells.

At the equator, sloths move so slow their backs grow green with algae.
We're cousins to sloths and algae both, our shared cartography of cells.

Reversed on film, black mold unfolds into reclining cats
and plants ungrow. O, to undo death by the photography of cells!

Henrietta's cells did something new. They kept alive and grew.
Poor and black: even immortal, subject to demography of cells.

It's all about the replications, the ways we grind together.
Intertwined in heat and viscous fluids, pornography of cells.

A mustard seed becomes a melon. Unborn, stillborn. The moon
tilts. We communicate by touch, by the sonography of cells.

Jellyfish in the bay, a fleet of cold, diaphanous pleats.
No brains or hearts, simply luminous choreography of cells.

My eyes have always been blue. My heart's been busted a time or two.
Who cares about poetry? Who cares about lexicography of cells?

Once the written word was code enough. Now nothing else spells
Sara but messages in my DNA's cryptography of cells.

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Sara Wainscott has an MFA in poetry from the University of Washington. She lives in Chicago and teaches writing at Columbia College. Her poems have appeared most recently in *Required*, *Columbia Poetry Review*, *The Journal*, and *Poetry Northwest*.

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Suggested Readings and Resources

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About the Contributors

Theme Issue Editor

Byram H. Ozer, MD, PhD, is a second-year resident in neurology at the University of California, Los Angeles. He received his MD and PhD degrees from the University of Wisconsin School of Medicine and Public Health and completed his internship in internal medicine at Good Samaritan Hospital in Cincinnati, Ohio.

Contributors

Jeffrey R. Botkin, MD, MPH, is a professor of pediatrics and medical ethics and associate vice president for research at the University of Utah in Salt Lake City.

Murray H. Brilliant, PhD, is the director of the Center for Human Genetics at the Marshfield Clinic Research Foundation and the principal investigator for the Personalized Medicine Research Project in Marshfield, Wisconsin. Dr. Brilliant conducts research on complex human genetic disorders.

Shawneequa Callier, JD, MA, is an assistant professor in the Department of Clinical Research and Leadership at the George Washington University School of Medicine and Health Sciences in Washington, D.C.

Timothy Chang is a MD-PhD student at the University of Wisconsin - Madison. His research focus is in translational biomedical informatics, particularly in prediction of disease, prognosis, and treatment response, which he hopes to apply to personalized medicine.

Wendy Foth is a research coordinator with the Center for Human Genetics at the Marshfield Clinic Research Foundation in Marshfield, Wisconsin.

Joan H. Fujimura, PhD, is a professor of sociology and professor of science and technology studies in the Robert F. and Jean E. Holtz Center at the University of Wisconsin - Madison. Dr. Fujimura studies the social and ethical aspects of genetics, molecular biology, biotechnology, and biomedicine. Her research has been supported by NIH's National Human Genome Research Institute, the National Science Foundation, and the University of Wisconsin Graduate School.

Geoffrey S. Ginsburg, MD, PhD, is the founding director for genomic medicine at the Institute for Genome Sciences & Policy, the founding executive director of the Center for Personalized Medicine, and a professor of medicine and pathology at Duke University in Durham, North Carolina.

Dov Greenbaum, JD, PhD, is an assistant (adjunct) professor of molecular biophysics and biochemistry at Yale University in New Haven, Connecticut, a nonresident fellow at the Center for Law and the Biosciences at Stanford University Law School in Palo Alto, California, and an attorney at Pearl Cohen Zedek Latzer in Israel.

Susanne B. Haga, PhD, is an associate research professor at the Institute for Genome Sciences & Policy and Sanford School of Public Policy and the director of education and training at the Institute for Genome Sciences & Policy, all at Duke University in Durham, North Carolina. She received a PhD in human genetics from the University of Maryland. Her research interests focus on the translation of genomic medicine, particularly pharmacogenetics, and the legal, regulatory, ethical, educational, and social implications of genomic research and applications.

Bruce Korf, MD, PhD, is a medical geneticist who is board certified in pediatrics, child neurology, medical genetics, clinical cytogenetics, and clinical molecular genetics. He is the Wayne H. and Sara Crews Finley Professor of Medical Genetics, chair of the Department of Genetics, and director of the Heflin Center for Genomic Sciences at the University of Alabama at Birmingham. He is immediate past president of the American College of Medical Genetics and Genomics and president of the ACMG Foundation for Genetic and Genomic Medicine.

Aaron M. Lowe, PhD, completed his doctoral studies in the laboratory of Nicholas L. Abbott, PhD, and Paul J. Bertics, PhD, with a focus on the detection of biomolecules through novel techniques.

John Mahoney, MD, is associate dean for medical education and an associate professor of emergency medicine at the University of Pittsburgh School of Medicine in Pennsylvania. His academic interests focus on innovation in medical student education and on improving the connections between students, faculty, and patients.

Rachel A. Mills, MS, is a clinical research coordinator and certified genetic counselor at the Institute for Genome Sciences & Policy at Duke University in Durham, North Carolina. She received her MS in genetic counseling from the University of North Carolina at Greensboro. Her primary research interests include public and professional genetics education and the use of genomics in health care.

Ramya Rajagopalan, PhD, is a postdoctoral research fellow in the Department of Sociology at the University of Wisconsin - Madison and an ethics fellow at the Morgridge Institute for Research. Dr. Rajagopalan (with Joan H. Fujimura, PhD) studies the social, ethical, and clinical impacts of genetics, biomedicine, and biotechnology.

Rachel Simpson is a graduate student pursuing a master of public health degree in epidemiology at the George Washington University School of Public Health and Health Sciences in Washington, D.C. She received a bachelor of science degree in

cognitive science with a specialization in neuroscience from the University of California, San Diego.

Sara Wainscott has an MFA in poetry from the University of Washington. She lives in Chicago and teaches writing at Columbia College. Her poems have appeared most recently in *Required*, *Columbia Poetry Review*, *The Journal*, and *Poetry Northwest*.

Carol Waudby is a research coordinator with the Center for Human Genetics at the Marshfield Clinic Research Foundation in Marshfield, Wisconsin.

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