Integrating Personalized Genomic Medicine Into Routine Clinical Care: Addressing the Social and Policy Issues of Pharmacogenomic Testing

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The provision of personalized genomic medicine presents significant policy challenges, such as ensuring equitable patient access to testing, preparing clinicians to manage genomic results, justifying test reimbursement, sharing genomic information for patient care, and protecting patients against misuse of genetic information.

Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?

T. S. Eliot, The Rock (1934)

Ten years after the completion of the Human Genome Project, we now have an incredible opportunity to apply the knowledge and technology gained from that effort. One of the most promising areas for translating genomic knowledge into routine clinical care is pharmacogenomics, which analyzes a patient’s genetic makeup to predict responses to drug therapy. Pharmacogenomic testing can provide a path for the expansion of individualized genomic medicine to optimize a patient’s health and can help to minimize the cost of care. However, implementing genomic testing to guide routine clinical decision making requires careful consideration of relevant social and policy issues, including the equitability of access to genomic tests and the preparedness of clinicians to use genomic information. These issues can either impede or facilitate successful integration of genomic information into clinical practice. They can also serve to drive public policy to support the implementation of such testing. Addressing these issues requires a transdisciplinary approach—one in which the goal is problem solving, rather than problem identification.

Clinical Utility of Pharmacogenomic Testing

Every individual inherits variations in DNA from each parent; these variations are passed down from generation to generation. When variations occur in genes that metabolize drugs, they can affect an individual’s response to these drugs. By identifying these variations, pharmacogenomic testing can help to prevent or minimize toxic side effects and to maximize a drug’s effectiveness. This information can be used to help guide clinical decisions—to choose a particular drug or drug dose, to select an alternate drug if one is available, or when no other drug is available, to carefully monitor drug response and provide supportive care to offset anticipated adverse events. Pharmacogenomic testing holds the promise of reducing health care costs (eg, by decreasing the number of hospitalizations for adverse drug events), avoiding unnecessary or ineffective therapy, and increasing patient adherence to drug therapy (because patients are more likely to comply with drug therapy that is effective and has minimal adverse effects). Although evidence-based data continue to be the most important factor influencing adoption of these tests in routine clinical practice [1], complex social and policy issues need to be addressed to ensure that all patients have the opportunity to benefit from clinically useful genomic tests (Table 1).

Consider the following clinical scenario:

A moderately overweight, 67-year-old white man with high blood pressure presents to his primary care physician with shortness of breath and a history of angina for the past 2 months. He is referred to a cardiologist and is seen in the cardiology clinic the following day, at which time cardiac catheterization is recommended. The cardiologist tells the patient that during the procedure it may be necessary to place a stent in his artery and to give him the antiplatelet drug clopidogrel. The patient is scheduled for a preoperative visit in 3 days. Although he has Medicare coverage, he is concerned about his finances, because most of the family’s savings have been spent on treatment and care of his wife, who has multiple sclerosis. The couple may have to apply for Medicaid soon.

How can pharmacogenomics be clinically useful in this setting? Testing to help determine the patient’s ability to metabolize clopidogrel may be helpful in this scenario. Clopidogrel is a prodrug that is converted to its active...
metabolite by the cytochrome P450 enzyme CYP2C19. Variations in the gene coding for the CYP2C19 enzyme can affect an individual’s ability to activate the drug [2]. Up to 25% of white individuals in the United States have a variant allele that may result in reduced effectiveness of clopidogrel or drug failure, leading to stent thrombosis and risk of embolism [3]. Clopidogrel is one of several drugs that are required by the US Food and Drug Administration (FDA) to have a black-box warning recommending that patients undergo genetic testing before being given the drug (Table 2). If the patient has DNA variations that are associated with an inadequate response to clopidogrel, then the cardiologist can select appropriate alternate therapies, such as prasugrel or ticagrelor.

Dissemination of Information to Clinicians

For the patient mentioned above to benefit from CYP2C19 testing, his clinicians must first be aware of the test and be prepared to utilize, interpret, and apply genomic test results to manage their patients. Numerous studies have indicated that physicians, pharmacists, and nurses do not feel well prepared to adopt and use pharmacogenomic tests [1, 4]. Clinicians need easy access to up-to-date, accurate information in order to determine the clinical usefulness and value of such tests for their practice and to decide whether and when to adopt these new tests. In 2009 the FDA recommended a change to clopidogrel’s prescribing label to reflect recent publications identifying associations between CYP2C19 variants and response to clopidogrel [5, 6]. Although clopidogrel is used in many settings, CYP2C19 testing has value mainly for patients with acute coronary syndrome who are undergoing percutaneous coronary intervention (PCI) [2, 7].

The rapid pace of knowledge generation and the distillation of its clinical value require keeping careful track of the literature and evaluating its clinical utility—which many physicians do not have time to do. Fortunately, some resources can aid the clinician in making these assessments, including 2 efforts funded by the National Institutes of Health: the Pharmacogenomics Knowledge Base (PharmGKB) and the Clinical Pharmacogenomimc Implementation Committee (CPIC). PharmGKB curates and synthesizes pharmacogenomic information in real time in a user-friendly database (http://www.pharmGKB.org). CPIC, a component of PharmGKB, consists of expert teams of clinicians who evaluate and publish guidelines for the interpretation and clinical application of pharmacogenomic test results [8]. Many of the CPIC guidelines relate to the drug-gene pairs associated with FDA black-box drug warnings (Table 2). However, additional resources for the clinician are needed. One option is to have point-of-care clinical decision support tools embedded in the electronic medical record (EMR); such tools can alert physicians to the existence of useful tests and can be systemized so that they are triggered at different points of care (eg, when the physician writes a prescription or when the pharmacist dispenses it) [9]. An in-house genomic medicine consultation service is another valuable resource [9]. Ideally, this service would be made up of an interdisciplinary team of experts who are available for education and for point-of-care evaluation and interpretation; these experts can work with a hospital’s pharmacy and therapeutics committee as well as with clinicians, health information technology, and laboratories to provide tailored support services. Each of these efforts, however, depends on the efficient dissemination of accurate information to a network of clinicians. It is essential that education, training, and communication programs be tailored to the needs of clinicians at the local, regional, and state levels; that these programs be coordinated; and that they be developed for all clinicians to access and use.

Use of Electronic Medical Record Systems to Optimize Care

Consider a different scenario for the patient mentioned above. Instead of going to see his primary care provider and getting a referral, what if this patient suffers an acute episode at home? Now, rather than undergoing an elective procedure, he is rushed to the emergency department and admitted to the hospital for an emergency cardiac stent procedure. In this scenario, assume the patient’s primary care physician knew about pharmacogenomic testing, had preemptively ordered a panel of tests during the patient’s most recent annual visit, and already had the test result showing a CYP2C19 variant associated with clopidogrel drug failure. Ideally, having interoperable EMR systems with a standard place for storing pharmacogenomic test results would allow the cardiology team to efficiently access this information at the point of care. The team could select an alternate ther-

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<th>TABLE 1. Policy Issues Related to Genomic Testing</th>
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<td>Need for interoperable electronic medical record systems</td>
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<td>Level of evidence needed for test approval, reimbursement, and endorsement</td>
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<td>Assessment of clinical value added in order to justify expenditure for genomic testing</td>
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<td>Need for protections</td>
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apy, saving time and money by not ordering a test that had already been performed. Although there are federal incentives to implement an approved EMR system with interoperable capacity, in 2012 only 48.3% of office-based physicians in North Carolina reported having an EMR system that met basic criteria [10]. Pharmacogenomic test results, when they are available, are often buried in laboratory information and are not readily accessible for patient care. Cost, logistics, and lack of informatics technology support are significant barriers to the broad implementation and use of interoperable EMR systems. Additional incentives and support for such systems beyond what has already been established at the federal level [11] are needed to address this issue.

Level of Evidence Needed for Adoption and Reimbursement of Testing

Education, training, and EMR systems are insufficient to support the use of pharmacogenomic tests if there is variability in the levels of evidence needed for their approval, reimbursement, and endorsement. The Centers for Medicare & Medicaid Services (CMS) reimburse in the outpatient setting for CYP2C19 testing and for each of the genetic tests mentioned in FDA black-box warnings (Table 2). Because third-party payers often follow the lead of CMS when making reimbursement decisions, CMS policy can have a significant impact on whether a test is covered. Although CYP2C19 testing is strongly recommended by the FDA and is reimbursed by CMS for outpatients, some professional groups have not fully endorsed this test as a standard of practice [12].

Some of this variability may reflect the different thresholds of evidence and varying definitions of clinical utility sought by each stakeholder. Some of the variability also reflects the different sources of information that each stakeholder uses to make these assessments. The decisions made by CMS or professional groups, and the processes and policies that drive them, significantly influence clinicians who are considering whether to adopt new tests. Some clinicians will adopt tests early, some later, and some not at all [13]. A minimum level of evidence and consensus regarding the relevant criteria needed to satisfy definitions of clinical utility will promote more consistent assessment of genomic information.

Access to Care, Resource Allocation, and Health Disparities

In the first scenario for the aforementioned patient, the cost of testing (approximately $250–$350) would likely be reimbursed by Medicare, provided that the test was ordered in the outpatient setting and was clinically indicated (eg, related to a likely future PCI). CMS will not reimburse for preventive screening of the variant without medical necessity. Since the patient in this scenario could be considered to be at high risk for a subsequent PCI intervention, the test should be covered. However, if this patient were a Medicaid recipient, reimbursement as an outpatient would depend on where he was living, because the processes and sources of information for Medicaid reimbursement coverage decisions vary from state to state. To make things even more challenging, once the patient is admitted to the hospital, CMS reimbursement is based on the diagnosis-related group (DRG) code for the procedure, not for each individual test.

How can physicians and hospitals justify using limited health care resources to support pharmacogenomic testing? Data from my institution, regarding projected CYP2C19 testing for inpatients undergoing a cardiac stent procedure involving clopidogrel, yielded the following conservative estimates of cost savings. For Medicare patients alone, cost minimization per year was estimated to exceed $500,000 (based on minimizing the length of the hospital stay and reducing 30-day readmission rates due to drug ineffectiveness). If these estimates and the evidence on which they are based are accurate, they support testing for all inpatients receiving cardiac stents.

A comprehensive economic analysis is understandably more complex. However, current economic models are insufficient to assess the potential impact of genomic testing, especially preemptive testing, which could affect an individual’s health and associated health care costs over his or her entire lifetime [14]. Furthermore, by federal statute, CMS is currently not allowed to reimburse for preventive services unless authorized to do so by Congress [15]. Models for economic analysis, including the benefit of preemptive testing over an individual’s lifetime, need to be developed and made accessible to members of Congress, physicians, and hospitals so that the impact of pharmacogenomic testing can be appropriately assessed.

A major concern related to the use of genomic information in health care is that it will exacerbate existing health disparities; this concern is especially relevant for states with large underserved populations, including North Carolina. The concern that testing will benefit only affluent patients and those with health insurance that covers the tests is borne out every day in other areas of health and genetics. As health care costs continue to grow and resources become even more limited, this continues to be a significant concern.

Subgrouping, Stigmatization, Discrimination, and Privacy

Although drug response can be related to a variety of nongenetic factors (eg, lifestyle, diet, cultural norms, environmental exposure, comorbid conditions, etc), the very nature of pharmacogenomic testing involves grouping patients based on genetic variations. Often these classifications or subgroups are associated with a particular ethnicity, ancestry, or geographic region of origin. Minimizing harm to already vulnerable populations can become even more challenging. When should markers of ancestry rather than race or ethnicity be used for testing decisions? When can ethnicity be useful?

To shed light on these issues, consider the drug carba-
GINA does not apply to life insurance, long-term care insurance, or most military personnel [19]. Furthermore, because GINA has been enforced by courts, significant limitations exist. GINA does not apply to employers with fewer than 15 employees or to most military personnel [19]. Although GINA offers many levels of protection of confidentiality of genomic information and an individual’s privacy. However, the protections offered when applying both the ADA and GINA are complex to interpret, especially regarding the language describing each law’s protections for “asymptomatic individuals” compared with individuals “with manifest disease”[23]. In addition, many states have laws that address the use of DNA (e.g., blood spot cards collected at birth) or in some way protect the confidentiality of genetic information or an individual’s privacy. However, laws in different states vary a great deal in the protections they offer [24]. In conclusion, I want to emphasize that the use of pharmacogenomic testing to guide clinical care is not futuristic. This testing is already a reality, and assessment and application of genomic information will increasingly be an integral part of patient safety and quality of care measures. As the provision of health care transitions from a fee-for-service to a value-of-service environment, these assessments will become even more important. I have touched on only a few of the myriad policy questions and potential approaches to addressing them. Many other questions exist, and more will emerge as genomic information becomes a more routine part of medical care. Who should have access to genomic information, and when should incidental findings be communicated to patients? Who should oversee the quality of testing, control the approval process for drug and test development, or disability insurance. Nonetheless, GINA is effective in minimizing misuse of genetic information.

The Health Information Portability and Accountability Act (HIPAA) provides privacy and security protections against unauthorized use or disclosure of personal health information, including genetic information [20]. HIPAA is not comprehensive protection, and many parts of this law are supplemented by GINA, especially in the employment setting. HIPAA applies to covered entities such as hospitals, health plans, and physician practices. HIPAA does not limit the disclosure of genetic information by insurers, nor does it apply to genetic information collected in some research settings, such as commercial industry [21]. The Americans with Disabilities Act of 1990 (ADA) [22] also provides some protection against discrimination on the basis of genetic information. In the employment sector, however, the protections offered when applying both the ADA and GINA are complex to interpret, especially regarding the language describing each law’s protections for “asymptomatic individuals” compared with individuals “with manifest disease” [23]. In addition, many states have laws that address the use of DNA (e.g., blood spot cards collected at birth) or in some way protect the confidentiality of genetic information or an individual’s privacy. However, laws in different states vary a great deal in the protections they offer [24]. In conclusion, I want to emphasize that the use of pharmacogenomic testing to guide clinical care is not futuristic. This testing is already a reality, and assessment and application of genomic information will increasingly be an integral part of patient safety and quality of care measures. As the provision of health care transitions from a fee-for-service to a value-of-service environment, these assessments will become even more important. I have touched on only a few of the myriad policy questions and potential approaches to addressing them. Many other questions exist, and more will emerge as genomic information becomes a more routine part of medical care. Who should have access to genomic information, and when should incidental findings be communicated to patients? Who should oversee the quality of testing, control the approval process for drug and test development, or disability insurance. Nonetheless, GINA is effective in minimizing misuse of genetic information.

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TABLE 2.
Drugs with US Food and Drug Administration Black-Box Warnings Recommending Genetic Testing Prior to Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genetic test</th>
<th>Drug use for which test results are relevant</th>
<th>Implication of presence of genetic variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701 variant</td>
<td>First- or second-line treatment of HIV/AIDS</td>
<td>Potentially lethal hypersensitivity reaction</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*1502 variant</td>
<td>Epilepsy, bipolar disorder, and other applications in individuals of Han Chinese ancestry</td>
<td>Potentially lethal hypersensitivity reaction, especially in individuals of Han Chinese ancestry</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19 variant</td>
<td>Antiplatlet therapy in patients undergoing percutaneous coronary intervention</td>
<td>Ineffective drug response; risk for stent thrombosis and other cardiac events</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6 variant</td>
<td>Pain management in children</td>
<td>Rare but potentially lethal response in children</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Chromosome 5q deletion</td>
<td>Hematology, myelodysplastic syndrome, multiple myeloma</td>
<td>Chromosome 5q deletion indicates risk for high-grade toxicity</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>PML/RARα fusion protein translocation</td>
<td>Oncology (multiple myeloma, acute promyelocytic leukemia)</td>
<td>Translocation predicts likelihood of drug response</td>
</tr>
</tbody>
</table>

opment, and give the pharmaceutical and biotechnology companies incentives to develop drugs and tests that target vulnerable populations, rare diseases, or resource-poor areas? As genomic medicine becomes integrated into our health care system, so too does the need to develop responsible policies and processes to address the associated social, economic, and information issues.

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