This article is the second in a three-part series on the topic of medicine that is geared toward the individual patient. Part 2 explores key ethical, legal, and regulatory issues facing the future of personalized medicine. Part 3 will cover the anticipated challenges in implementing pharmacogenomics and genetic testing into routine clinical practice.

Key words: ethical, legal, and regulatory; health plans and coverage, HIPAA Privacy Rule, Protected Health Information, GINA, HITECH

ETHICAL CONSIDERATIONS
Can Ethics Drive the Health Care System To Do No Harm?

Modern medicine has no doubt extended patients’ lives and improved health quality of life. Yet our nation’s health care system represents a moral failure. Despite a plethora of diagnostic modalities and treatments, life spans are lower in the U.S. than in comparable countries. Access to care remains difficult for patients and is often a burden on the system. Cost containment seems unattainable, both for research and development (R&D) and for clinical use, particularly for new technologies such as personalized medicine (PM).

The efficacy of prescribed medicine hovers around 50% to 60% for most common ailments and is only 20% for cancer therapies. Molecular biology is demonstrating the failure in both a one-size-fits-all model and a more “personalized” model. Scientific advances have demonstrated the possibility of identifying risks for disabling health problems, choosing the treatment strategy most likely to benefit specific patient groups, and mitigating risk by reversing the processes that cause disease. In this way, PM is a vital strategy in the effort to provide better health care and decrease overall costs. It is vital, in that affordable and effective health care is fundamental to the nation’s quality of life; health care costs continue to escalate, including the cost of prescribing too many drugs that are neither safe nor effective.

Unsafe and ineffective drugs cause avoidable deaths; adverse reactions, many of which result in costly hospitalizations; and wastage resulting from discarding medications that don’t work. According to the Agency for Health Care Research and Quality (AHRQ), adverse reactions result in more than 770,000 injuries and deaths each year and cost up to $5.6 million per hospital, depending on size.1 A report from the National Academy of Sciences, published in 2009, emphasized the need to apply a new approach to allow monitoring of each patient’s health status and to treat any malfunction in a manner that is tailored to that individual.2 Thus, the promise of PM, if fully realized, has the potential to significantly influence the nation’s health care.

We are inching our way to pharmacogenomics-based prescribing, and we can now offer tests to determine whether patients might benefit from certain drugs—for example, warfarin (Coumadin, Bristol-Myers Squibb), the protein thiopurine methyltransferase (TPMT), and several tricyclic antidepressants (TCAs); however, such testing is, for the most part, research-based. In two or three cases, though, the FDA has required testing prior to drug administration, as in the case of trastuzumab (Herceptin, Genentech), yet test-based prescribing is far from the standard of care. In the coming years, advances in pharmacogenetics will convert the “art” of prescribing into a “science,” and with this knowledge, we will no longer need to rely on the dangerous methods of trial-and-error prescribing. Current methods of determining the safety and efficacy of medications, in other words, will eventually become a historical footnote.

Today we face significant challenges in adopting safe and effective, personalized diagnostic and therapeutic approaches. Physicians will be the key to achieving the promise. Although tests and companion diagnostics exist to improve prescribing and care outcomes, physicians typically do not have the detailed analyses of clinical information needed to select optimal drug treatments and dosages on the basis of a patient’s unique genetic profile, physiology, and metabolic processes. In the absence of what is needed to know to deliver PM, physicians can easily continue to use a certain amount of trial-and-error methods when they evaluate treatment approaches.

Why Ethics Is Pivotal to Success

In keeping with their Hippocratic oath, physicians are obligated to do no harm, yet prescribing practitioners usually have no way of knowing in advance whether a drug they prescribe will harm a patient. Therefore, we can ask whether physicians are fulfilling their duty to do no harm when the prescribing information about how particular medications affect their patients is so meager.

Although it is unlikely that patients would be refused health insurance because they do not respond to a specific drug or because a particular drug formulation is toxic to them, the possibility that insurers would require genetic testing to determine drug safety and efficacy, so as to avoid unnecessary cost burdens, is sensible from a cost perspective but ethically indefensible if individuals are coerced. It is easy to imagine why Medicaid or Medicare would want to require such as a condi-

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tion of program participation. Even though this scenario is probably uncommon, individuals might prefer to incur the risks associated with trial-and-error prescribing in order to avoid a greater personal risk that their genome information might be generated—along with the possibility of unauthorized access or worse. Such a situation raises the question of whether genetic testing might be required, thereby compromising an individual’s right to refuse and further imposing unwanted information associated with other health risks if the gene variant was associated not only with drug response but also a significant health risk.

For example, safety laws and public policies may require a seat belt, a helmet, or even restrictions on elderly drivers. Whether an individual’s right to autonomy is primary and, therefore, a greater ethical requirement than society’s right to maintain efficient and effective care, or a payer’s right to avoid unnecessary cost burdens, remains problematic and illustrates a core issue in integrating PM into clinical care. Who should control access to new pharmacogenetic and pharmacogenomic tests and companion diagnostics?

An important ethical question involves determining what entity ought to control access to tests (payers? physicians? the government?) and why. Should criteria regarding access remain as they are, particularly if our current health care system remains substantially unchanged?

Currently, we have disparities in coverage, ability to pay, knowledge of availability of testing, and physicians’ knowledge and their comfort level in using it. Should individuals be free to buy and use new tests even if they are not approved by the FDA or regulated in any way? Should we trust industry to market tests that meet the strictest standards, including those that may be voluntary, if strengthening regulation and enforcement thereof proves slow and costly?

On the one hand, patients have a right to information that can affect their care, and they may well demand that testing be available despite cautionary objections from a conservative medical community that requires evidenced-based benefits. Still, patient demand will probably be mitigated by ability to pay, as health care institutions will be reluctant to pay for tests unless or until the cost-benefit and cost-effectiveness ratio is solidly proven. Practitioners’ acceptance and resulting use of testing will undoubtedly be influenced by their degree of confidence in new approaches—doctors are very slow adopters of innovative technology—and their need for endorsements from organizations that set clinical standards.

Pitting physician reluctance against patient demand requires broadening most policy discussions of harms and benefits. Such debates focus primarily on the merits of scientific findings and the basis for proof. Rarely do such discussions consider the harm that results from approved regulated drugs that clearly can cause such horrific effects that they are (voluntarily or involuntarily) withdrawn from the market. We must address the risk–benefit issue directly and properly frame these problems for participatory discussion.

Medical advice has long been the product of “cookbook” approaches, with patient reporting being the key to determining the right treatment. However, we now find ourselves at an interesting juncture where medical care standards require evidence-based proof, yet the responsibility for and the cost of maintaining one’s health is increasingly being borne by individuals themselves. Patients, therefore, having an increasingly greater stake in the outcome of such policy and regulatory debates. The benefit to patients, and to society at large, may well be sufficient to permit wide usage of these technologies sooner rather than later. The payoff could be great, and the potential for genuine harm could be quite low.

Within families, whose right to knowledge ought to dominate? Should parental prerogatives always trump the consent of minors? Can we justify statutory differences in the legal age of consent? What about the competing rights of identical twins? What about family members who run the risk of unauthorized access to their private genetic testing results?

The recently enforced regulations of the Health Insurance Portability and Accountability Act (HIPAA) could obviate some contentious privacy battles, particularly those arising within immediate families, by requiring all patients to consent to disclosure of private health information and to authorize access to specific third parties (see page 628 for more information on HIPAA). Genetic information is particularly susceptible to privacy violations, simply because it reveals facts not only about the individual who underwent testing but also about certain blood relatives. The limit of an individual’s right to consent to genetic testing was itself examined a few years ago in an interesting case.

The father of a research subject opened a letter addressed to his daughter, a consenting adult who had enrolled in a genetic research study. The daughter had obtained the father’s medical record, as per protocol. The father fought the disclosure of his medical information because he had not consented to such a disclosure. The National Institutes of Health (NIH) halted the research study until protocol-related changes regarding consent were developed.

The Office of Human Research Protections blocked access to the father’s information on the grounds that an individual’s right to privacy and autonomy was paramount, whether or not the information had or could have a direct bearing on the daughter’s clinical care. Furthermore, an individual’s medical history, which can increasingly include the family history and genetic test results, is frequently disclosed informally on surveys without other family members’ consent.

Among the interesting and difficult issues in this case is the fact that it challenges us to think deeply about the weighted values we assign to first principles, namely the right to privacy. Whose right is primary? What are the limits of entitlement, and why?

Although research regulations determine protection policies and procedures for human subjects, the dramatic success of targeted therapies is likely to lead patients in experimental groups (in which treatment is found to be ineffective) to allege wrongdoing and to lead medical researchers to refuse to give patients treatments that are shown not to work. Lawsuits have been, and most likely will continue to be, filed when patients allege serious wrongdoing. Because the amount of data required to enable PM on a broad scale will be expanded, ethical dilemmas are likely to continue to arise from data security mishaps.

Can principles of justice ensure a fair distribution of the benefits and burdens of PM?
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The truly transformative power of PM is widely recognized. Knowing whether a drug will be safe and effective for individual patients will enable them to avoid medications that are dangerous or ineffective. Although such an advance seems clearly desirable and cost-effective, and also morally obvious, achieving widespread benefit may be difficult, in part because PM can work only if the health care system changes to adapt to the potential of PM.

Such achievements are consistent with attaining greater justice. Patients will be less financially burdened because they will not have to keep spending scarce dollars on drugs that don’t work. Drugmakers will earn less money from supplying drugs that result in adverse events. Unless all stakeholders are persuaded that delivering the right treatment to the right person at the right time is the highest priority, justice will not be served. This is because pharmacogenetic and pharmacogenomic knowledge, in demonstrating the right therapeutic strategy, induces patients to know that they deserve better. Whether patients can get what they believe they deserve will depend on whether systemic barriers are removed. Barriers often leave the promise of PM unfulfilled. The most intractable obstacle is the misaligned interests and incentives among the following entities:

- The pharmaceutical industry is reluctant to adapt because PM reduces the market size and profits associated with their blockbuster one-size-fits-all drugs.
- Insurers resist change because the return on investment of expense diagnostics and therapeutics is simply not there. Disease prevention doesn’t pay, although coverage is beginning to take hold in some cases.
- Physicians are not poised to practice PM because the best diagnostic and therapeutic strategy is not yet supported in clinical standards or evidence-based medicine.
- Patients could be a potent driving force, but specific groupings of advocates do not yet exist and access is not being demanded.
- Regulators continue to debate about how best to handle new and anticipated complexities and about the extent to which agencies have the legal authority to create new rules.
- Even while the diagnostic industry is growing, reimbursement is not keeping pace; that is, stakeholders’ interests compete in ways that discourage mutual benefit.

Also problematic is the fact that biomedical tests and therapeutics are available within a health care system that has widespread inconsistencies and practices; test standardization does not exist. Tests from one laboratory are not comparable to those from another laboratory. This variability is considerable; at least 2,700 genetic tests are available, but standards exist for only 35 analyses. Regulatory compliance permits each manufacturer to apply internal standard references and general control reagents.

Ultimately, the current system is not poised to serve the goals of either PM or ethics. Ensuring that patients receive the treatments they need depends on their ability to undergo the right tests, yet access is restricted by numerous constraints. Physicians and patients are rarely cognizant of the fact that a test from one laboratory is not necessarily equivalent to the same test performed at another laboratory, so choosing the best test is compromised by both a lack of awareness of test variations as well as payer constraints on coverage. Similarly, most consumers do not know that newborn screenings, as well as cutoff points, vary by state. There are between 29 and 54 tests, depending on one’s residence, which means that residency determines which disorders will or won’t be identified at birth.

Such realities raise questions about whether informed consent truly exists. Furthermore, if standards cannot reassure physicians and patients that care is based on certitude, the goals of PM are unlikely to be achieved and principles of justice will also be unmet. At issue are these questions:

- Who will really receive the benefits of PM?
- Will patients with private insurance and greater disposable income have unfettered access and better health care?

Especially because the cost of companion diagnostic testing is high, and given that it is in society’s best interest to ensure that better care and personalized disease-prevention strategies are available, this seems like an inevitable reality. In light of budget deficits and financial constraints, it is possible that state governments will require Medicaid recipients to undergo pharmacogenomic testing to avoid spending large sums of money on drugs that don’t work or that are likely to cause serious and even life-threatening events. Because history is replete with examples of states invoking new technologies to solve social ailments, this possibility is not so far-fetched.

For example, in several states, paternity testing is required as a way of identifying fathers to get them to pay child support to single mothers. Eliminating voluntary consent for a greater social good, this practice would pit an individual’s basic right against one stakeholder’s attempt to seek the “greatest good” and represents a contemporary example of a clash between deontological and utilitarian principles. Some patients, also seeking to achieve the greatest good, have helped companies understand genotypic–phenotypic relationships by participating in clinical trials designed to develop safe, effective treatments. After such treatments are commercially available, they frequently come with enormous price tags, with the result that the lifetime insurance reimbursement cap of $1 million is reached very quickly. Patients are left to pay out of pocket—if they can pay at all.

Securing public interest and trust is crucial to enabling PM to realize its goals. Furthering such goals requires expanding genotypic–phenotypic data; however, if PM is to be realized, it is essential that this genetic–phenotypic information be treated as strictly confidential and be inaccessible to unauthorized entities.

Certainly, ethics is the cornerstone of enabling the advancement of PM. A properly randomized clinical trial can be viewed as unethical, raising questions about how to handle nonresponders and about the type and quantity of data that are good enough to influence practice standards.

For justice to be achieved, so-called ethnic therapies must be supported by sound science. Scientifically justified groupings of subpopulations, along with guidelines for defining such groupings, are necessary, lest injustices result from perpetuating continued on page 628
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...ating racial and ethnic exclusions. Isosorbide dinitrate/hy- 
dral-azine (BiDil, NitroMed), for example, was heralded as the 
first race-based drug. In practice, however, it was marketed to 
self-identified African Americans with congestive heart failure, 
raising serious concerns about the scientific underpinnings of 
“race” as well as ethical issues around marketing an expensive 
drug that patients could obtain in less expensive generic forms. 

Similarly, Caucasian and Asian women are at the greatest 
risk for osteoporosis. Carbamazepine (Tegretol, Novartis) 
carries the same risk of renal complications as the immuno-
suppressive drug cyclosporine (e.g., Sandimmune, Novartis). 
Rosuvastatin (Crestor, AstraZeneca) may pose a greater risk 
for muscle injury for these patients than in the rest of the in-
dicated population. The FDA warns that certain drugs for 
epileptic seizures may prompt a severe skin reaction in Asian 
patients because of a genetic trait. 

Despite the lack of scientific evidence for so-called race-
specific drugs, political and medical discourse has yet to com-
municate such clinical information in ways that do not reinforce 
the misguided notion that genomic medicine scientifically 
legitimizes existing racial or ethnic phenotypic differences. We 
need better language for determining appropriate classifica-
tions and for communicating such differences in ways that do 
not revert to the kinds of racial and ethnic injustices that have 
occurred in the past. 

In summary, attention to ethical issues is essential to the 
success of PM and, ultimately, to the health and well-being of 
us all. 

LEGAL AND REGULATORY CONSIDERATIONS

Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act of 
1996 (HIPAA) was enacted to ensure that personal medical 
information stored, accessed, or processed adheres to a set of 
privacy guidelines. These security rules outline measures to 
safeguard all electronic Protected Health Information (PHI). 

More than a decade ago, the Congress, called for a set of federal 
standards, now known as the HIPAA Privacy Rule, to protect 
personally identifiable medical data while still allowing the 
flow of information needed to promote high-quality health 
care. The HIPAA law has its roots in the Clinton health care 
reform proposal of 1993, and its primary purpose was to pro-
vide better access to health insurance as well as to toughen the 
law concerning medical billing fraud. Other corollary sections 
of the HIPAA law are related to administrative simplification 
and privacy of PHI that have far-reaching effects for health care 
providers, insurance companies, managed care organizations, 
their business associates, and any entity that stores, processes, 
or transmits health care information. 

HIPAA amends the Internal Revenue Code of 1986 by: 

- improving portability and continuity of health insurance 
  coverage for groups and individuals 
- combating waste, fraud, and abuse in health insurance and 
  health care delivery 
- promoting the use of medical savings accounts 
- improving access to long-term care services and coverage 
- simplifying the administration of health insurance 

HIPAA compliance also includes provisions for improving 
and monitoring the security and confidentiality of any health 
plan members’ and patients’ medical records. In 1998, the De-
partment of Health and Human Services (DHHS) proposed, 
as part of these HIPAA provisions, a National Standard 
Provider Identifier (NPI), a National Standard Employer Iden-
tifier (EIN), and security standards for electronic health data. 
The Administrative Simplification Rules of HIPAA are intended 
to improve efficiency in health care delivery through stan-
dardized, electronic transmission of many administrative and 
financial transactions and protection of confidential health 
information. 

In a 2009 report, the Institute of Medicine concluded that the 
HIPAA Privacy Rule does not protect privacy as well as it 
should and that, as currently implemented, it impedes impor-
tant health research. 

American Recovery and Reinvestment Act of 2009

According to Doug Peddicord, Executive Director of the 
Association of Clinical Research Organizations, a new set of 
federal privacy and security requirements, introduced by leg-
islation promoting the adoption of electronic health records 
(EHRs), “may make the clinical investigator–clinical research 
organization interface more complicated for some time.” The 
new data-use restrictions “go well beyond the privacy rules 
established by HIPAA in 1996 and constitute a de facto transi-
tion to what came to be known as HIPAA-2,” he said. 

The sentinel event was President Barack Obama’s signing 
of the so-called stimulus bill, formally known as the American 
Recovery and Reinvestment Act (ARRA), on February 17, 
2009. The bill provided more than $19 billion in incentives for 
physicians and hospitals to use EHRs, and it made dozens of 
alterations to HIPAA-1, according to Mr. Peddicord. Some pri-
vacy and security requirements have been extended to com-
panies, such as Microsoft and Google, which offer personal 
health records (PHRs). The definition of PHR could be ex-
panded to capture patient registries, clinical trial portals, dis-
ease group databases, and various Web sites where consumers 
could go and voluntarily fill out a personal health survey. 

The stiff financial penalties for noncompliance reflect con-
gressional response to lackluster enforcement of the original 
HIPAA despite tens of thousands of complaints filed with the 
DHHS. Unlike HIPAA-1, HIPAA-2 makes business associates 
that work for covered entities “directly subject to the security 
rule and relevant provisions of the Privacy Rule,” says Mr. 
Peddicord. That specifically includes entities that transmit or 
process data on behalf of covered entities, such as regional 
health information organizations (RHIOs) and e-prescribing 
gateways. This new body of entities addressed by HIPAA-2 may 
see its newfound obligations regulated by the Federal Trade 
Commission (FTC) rather than the DHHS, “presaging a much 
stronger emphasis on enforcement,” according to Mr. Peddi-
cord. 

Language in HIPAA-2 that was intended to prohibit doctors 
and hospitals from selling PHI could be construed as barring 
covered entities from remuneration for constructing databases 
containing a limited set of “anonymized” patient information, 
says Mr. Peddicord. If covered entities have no financial 
incentive to do the work, public health activities and research
A central concern among providers is that even when information qualifies as de-identified and thus falls outside the HIPAA Privacy Rule, it could possibly be re-identified by computer “geeks” or hackers after it is posted on the Internet. The DHHS is thus likely to issue guidance encouraging more rigorous de-identification of PHI within the year that “may render data more expensive and/or less useful.”

Covered entities may have enough trouble coping with potential liabilities introduced by their new “breach-notification” obligations under HIPAA-2, says Doug Peddicord, which requires them to inform individuals whenever any piece of their PHI is lost or stolen. Similarly, business associates are obliged to report such breaches to covered entities. The breach-notification requirement took effect September 23, 2009, but almost all other HIPAA-2 changes became effective February 17, 2010.5

Health Information Technology
For Economic and Clinical Health Act

The DHHS has issued regulations requiring health care providers, health plans, and other entities covered by HIPAA to notify individuals when their health information is breached. These regulations implement provisions of the Health Information Technology for Economic and Clinical Health (HITECH) Act, passed as part of ARRA.

The regulations, developed by the Office for Civil Rights (OCR), require health care providers and other HIPAA-covered entities to promptly notify affected individuals of a breach and to alert the DHHS Secretary and the media if a breach affects more than 500 people. Breaches affecting fewer than 500 individuals will be reported to the DHHS Secretary annually. Business associates of covered entities must notify the covered entity of breaches. A Web site is available for tracking the progress of DHHS activities related to the ARRA (www.hhs.gov/recovery).6

As a result, medical practices must comply with the updated HIPAA privacy and security regulations that accompany ARRA and the HITECH Act, which went into effect in February 2010. The increased enforcement includes new breach-notification laws that impose fines if the act is not enforced; stricter accountability for business associates; and the use and disclosure of PHI. This has implications for all health care stakeholders who use, process, or work with any patient-level data generated by the health care system, including PM and its components.7

Genetic Information and Nondiscrimination Act

Several key acts of federal legislation provide the foundation for protecting medical and genetic information in the U.S., including:

- the Americans with Disabilities Act (ADA) of 1990 (42 U.S.C. § 12101 et seq.).
- HIPAA of 1996 (42 U.S.C. § 1320d et seq.).

The last act in this list strikes a balance between facilitating exchange of medical records among health care providers and public health officials and the need to ensure privacy of personal medical information.

HIPAA rules filled some gaps in protections against discrimination by shielding workers from unauthorized disclosure of their medical information to employers. However, insurers may still request genetic information or may require genetic testing of those applying for a health insurance policy. Enforcement of HIPAA rules is also fairly weak, relying solely on administrative action.

The Genetic Information Nondiscrimination Act of 2005 (GINA) explicitly prohibited employers and health insurers from discriminating against individuals on the basis of their genetic risk factors, thus filling certain gaps in HIPAA privacy protections.8

Signed into law May 21, 2008, by President George W. Bush, GINA overcame key barriers to moving PM forward. Thanks to GINA, genetic information cannot form the basis of health insurance underwriting decisions, and employers cannot use it to make hiring, firing, and promotion selections. Forbidding health insurers and employers from using genetic information means that privacy concerns about health information technology (HIT) also dwindle, as do similar concerns about biobanks.

The passage of GINA was important to stakeholders in research too. The possibility of genetic discrimination hindered progress in PM by hobbling basic research into the genetic aspects of disease.9

- There had been concern that employers and health insurers would have access to the results of genetic tests; this could keep people from asking their physicians for those tests, resulting in an inability to predict and prevent diseases.
- It was feared that genetic information obtained from participation in research studies would fall into the hands of employers and health insurers; this could deter people from enrolling in genetic research studies.

In the proposed and interim final rules (the Rules) published in the Federal Register on October 7, 2009, the DHHS and other agencies sought to strengthen patient protection provided under GINA. The DHHS, working with the U.S. Department of Labor and the U.S. Department of the Treasury, proposed to modify the HIPAA Privacy Rule (1) to state that genetic information was health information for purposes of the Rule and (2) to prohibit health plans from using or disclosing PHI, which would include genetic information, for underwriting purposes. Although GINA’s prohibition on using or disclosing genetic information for underwriting purposes currently applies only to certain health plans, the DHHS also clarified in the Rules that such prohibitions apply to all health plans that are subject to HIPAA.

When announcing the Rules, DHHS Secretary Kathleen Sebelius stated that by protecting Americans undergoing genetic testing from having the results of such tests used against them by their insurance companies, consumer confidence in genetic testing can now grow and help researchers get a better handle on the genetic basis of diseases.
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Genetic testing will encourage the early diagnosis and treatment of certain diseases while allowing scientists to develop new medicines, treatments, and therapies.

Under the Rules, health plans and health insurance companies, in both group and individual markets, cannot request, require, or buy genetic information for underwriting purposes before or during enrollment. Thus, insurers cannot increase premiums, deny coverage, or exclude applicants with preexisting conditions based on genetic information. Specifically, GINA prohibits:

- medical insurance companies from discriminating against applicants on the basis of their genetic information.
- medical insurance companies from requesting that applicants for health coverage plans be genetically tested.
- employers from using genetic information to refuse employment and from collecting such data.

Health plans also are generally prohibited from asking individuals (or family members) to undergo genetic testing. Many believe that this privacy protection for genetic PHI will promote participation in genetic research and therapies by insured patients who might otherwise avoid them for fear that results could be adverse to their insurance premiums and coverage. Violations of this proposed rule could result in a monetary fine for the unauthorized use or disclosure of genetic information.

Although GINA is not perfect, it provides several safeguards. There are still some limitations; for instance, it does not prohibit life insurance and long-term care insurance companies from using genetic information, and it protects only patients who have a genetic predisposition, not those with a diagnosed disease. Even with these concerns, GINA represents a big step toward enabling people to take advantage of the predictive knowledge of genetic research.10

MIXED MESSAGES: MOVING FORWARD

Industry is awaiting a definitive guidance on the codelopment of pharmaceuticals and diagnostics. Business models for drugs and diagnostics have traditionally taken a path of separate development; however, adaptation of business models to the new reality of linked development, as well as the diagnostic and drug products meant to benefit patients, will likely be delayed until the FDA clarifies its expectations for combination product clinical trials and regulatory submission.

The diagnostics industry is concerned that two recently released guidelines might inhibit the development of tests profiling multiple biological entities, such as proteins or genes. These documents are the Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays and the Draft Guidance for Industry and FDA Staff for Commercially Distributed Analyte Specific Reagents (ASRs). Such tests are currently regulated under provisions of the Clinical Laboratory Improvement Amendments (CLIA), which cover laboratory-developed or “home brew” tests that are provided not as a kit but as a service offered by a clinical reference laboratory.

In contrast to the CLIA provisions, the FDA regulatory path-way requires a careful premarket review of its analytical accuracy as well as its clinical validity. Although some manufacturers see the proposed regulation as potentially hindering the development of new products that already have controls on analytical and clinical validity, as well as clinical utility through market forces, others see the potential for new regulations to level the playing field and foster greater confidence (and reimbursement) for well-validated products.

Industry players have tried to address quality control in complex genetic tests by advocating for a genetics subspecialty within CLIA to ensure that laboratories meet certain standards. Federal advisory committees had recommended such a step as long ago as 1988.

In 2000, the DHHS published a notice of intent to propose a rule to create a genetic testing specialty, and in April 2006, the Centers for Medicare and Medicaid Services (CMS) placed the issuance of a proposed rule for a genetic testing specialty on its semiannual regulatory agenda. According to the Personalized Medicine Coalition, the creation of a genetic testing specialty under the CLIA would help to ensure the accuracy and reliability of the tests as well as personnel technical proficiency, increase the public’s trust in genetic testing, and promote the promise of PM.8

BARRIERS AFFECTING THE AVAILABILITY OF PERSONALIZED MEDICINE

On May 19, 2010, it was announced that Henry A. Waxman, chairman of the House Committee on Energy and Commerce; along with ranking member Joe Barton; subcommittee chairman Bart Stupak, also on the House Committee of Energy and Commerce; and subcommittee ranking House member Michael C. Burgess sent letters to three testing services—23andMe, Inc., Navigenics, and Pathway Genomics Corporation—because of reports that at least one of these companies was seeking to sell personal genetic testing kits in retail locations, despite concern from the scientific community regarding the accuracy of test results. The committee requested the following information from the companies:

- how test results are analyzed to determine consumers’ risk for any conditions, diseases, drug responses, and adverse reactions
- whether the tests were able to accurately identify any genetic risks
- policies for gathering, storing, and analyzing individual genetic samples collected from consumers

On May 20, 2010, following several weeks of on-and-off reporting of retail product availability, CVS Caremark, the largest provider of pharmacy services, followed Walgreens’ decision not to sell the Pathway Genomics genetic test kit. This decision resulted from an FDA notification to the company that its sample collection kit required FDA clearance. The FDA appears to have chosen this as a test case for future and evolving regulations regarding direct-to-consumer testing.

Several home sample collection kits are already on the market from Home Access for HIV infection and Flexsite Diagnostics for glycosylated hemoglobin (HbA1c) in diabetes. In addition, the FDA has not clarified regulations regarding
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laboratory-developed tests, which are being sold by Myriad Genetics, Genomic Health, and others.

THE FDA’S COMMITMENT TO PERSONALIZED MEDICINE

Incorporating PM into the U.S. health care system is a process rife with complexities. In February 2010, however, FDA Commissioner Margaret Hamburg outlined some initiatives aimed at surmounting a few of the primary obstacles. At the Sixth Annual Keynote Luncheon Address on the State of Personalized Medicine for the Personalized Medicine Coalition, she discussed three cardinal challenges:

• a more flexible regulatory path for PM with a product¬approval process that adapts to targeted genomic and clinical data
• a collaboration between government research and regulatory agencies
• transparency efforts among industry, the FDA, and the patient community in order to maximize the safety and effectiveness of personalized therapies as they are developed and move to the marketplace

The strategies are in accord with many recommendations in a report by the Personalized Medicine Coalition from 2009.11 Notably, three key plans are under way:

1. The FDA will focus its regulatory approach to adapt to the emerging science of PM. Dr. Hamburg described the FDA’s plans to build on previous successes by issuing new draft guidance on the identification of biomarkers. This step will give therapy developers a better idea of how to submit data on genes and proteins to the FDA so that therapies can be tailored to patients with specific biomarker profiles. She also encouraged the development of new clinical trial designs through university centers of excellence for regulatory science.

Dr. Hamburg touted the success stories of the past few years, such as genetic tests that can help calibrate the correct doses for the anticoagulant warfarin and the HIV drug abacavir (Ziagen, GlaxoSmithKline). In the case of abacavir, a genetic test is required to determine whether a patient has a form of the virus that will respond to the drug.

She also described the fruitfulness of the FDA’s Voluntary Genomic Data Submission Program. Since its inception in 2005, industry has warmed up surprisingly well to the program by submitting substantial amounts of data on the relationship between drugs and genes.

Dr. Hamburg emphasized that in order to ensure the safety and effectiveness of these new personalized technologies, the FDA must adopt an approach to monitoring the entire life cycle of a product, which necessitates postmarket follow-up research. The FDA plans to devise postmarket research protocols; when they are established, regulators and businesses will become more confident about the preapproval process.

2. The FDA is forming crucial collaborations with other agencies. The day before her address to the Personalized Medicine Coalition, Dr. Hamburg joined NIH Director Francis Collins and DHHS Secretary Sebelius to announce a new collaborative effort between the NIH and the FDA, designed to advance regulatory science. She also explained that the FDA and the AHRQ have discussed some research topics. More controversial, an audience member questioned her about the possibility of collaboration between the FDA and the CMS, which determines payments. We regard this as an important way for the FDA to gather information about the real-world usage of drugs and medical devices and for companies to have a better idea of the economic viability of their products, as has been done with the genetic tests surrounding warfarin, which are paid for only if the patient is part of a clinical trial.

3. The FDA is making its procedures more transparent. Dr. Hamburg acknowledges that coordination between the CMS and the FDA might raise concerns because the reimbursement rates determined by the CMS heavily influence the profitability of drugs and diagnostics. However, she said that the FDA would need to clearly explain to the public the scientific evidence and administrative rationale behind the decisions that these agencies make. Along with greater flexibility and collaboration, she considers the transparent sharing of evidence and explanation of policy rationales as one of the major components of the FDA’s modernization.

One of the more logically complex issues for the future of PM is the need for coordination between makers of genetic tests, drug manufacturers, and health care providers. For instance, Dr. Hamburg described the FDA’s “scenario-based” approach to “companion technologies,” such as a genetic test that is coupled with a drug whose effectiveness on a patient can be determined by the test results. Although some drugs and diagnostics will be developed in tandem, others will follow separate paths through different companies. She acknowledged that this would require a procedure by which various companies can be made aware of all the data coming into the FDA from different sources that may be relevant to each specific product.

CONCLUSION

In this 2nd part of our series, we have explored several key ethical, legal, and regulatory issues facing the future of personalized medicine (PM). Specifically, there are a variety of ethical issues that remain unresolved regarding the use of PM diagnostic or treatment products. This area becomes further clouded by the companion use of PM products in addition to new technologies that have not been seen in the marketplace before by consumers or clinicians. As we move out of the basic and early stage research environment with an ever increasing array of PM products, there will be a greater societal interest in debating and resolving these ethical concerns.

Along with the 2010 health reform legislation, there have been other key pieces of federal legislation that will have broad-reaching implications on the future of PM along with their use in the marketplace by clinicians. Both legislative and regulatory expansions to HIPAA, along with HITECH, will require clinical practice as well as health system adjustments to maintain information privacy or face stiffer penalties for failing to do so. Similarly, GINA expands the coverage of patient testing in a variety of marketplace applications beyond clinical medicine to include the workplace. Benefit managers, along

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with insurance and health plans, are now more directly at risk for inappropriate business practices related to consumer health testing or information.

Finally, a trend toward coordination among federal agencies beyond past cooperative practices may further complicate the marketplace dynamics for PM manufacturers as well as for clinicians. While it may still be too early in the evolution of health reform regulation now, given the number of high-level agencies and their regulatory bodies in addition to approximately 150 oversight groups in the health reform legislation, it is probably safe to say that following this trend among agencies will be important for all health care stakeholders in order to determine safe harbors for research and daily business practices.

REFERENCES