



Genetic Testing and Government Regulation: The Growing Significance of Pharmacogenomics

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**GENETIC TESTING AND GOVERNMENT
REGULATION: THE GROWING SIGNIFICANCE
OF PHARMACOGENOMICS**

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ABSTRACT: Genetic testing, currently a diagnostic tool used by only a small fraction of the population, promises to become a routine and critical part of medical care and drug prescription in the near future. This change will come chiefly through improvements in pharmacogenomics, the use of genetic testing to tailor medical care to an individual's unique genetic makeup. Current regulation of genetic testing is inadequate to meet the challenges of this new regime. Federal regulatory agencies, and in particular the FDA, are currently unprepared for the dramatic increase in scope and complexity of both the prescription drug market and the genetic testing market that is likely to result from the rise of pharmacogenomics. Although government advisory committees and legal scholars have long called for reform of genetic testing regulation, they have focused excessively on the moral dilemmas raised by predictive genetic testing at the expense of the increasingly significant area of pharmacogenomic research. This article provides a brief description of genetic testing, pharmacogenomics, and the current regulatory system, and highlights several areas where change is long overdue.

With the announcement in 2000 that several research teams had completed a rough map of the human genome, widespread use of genetic testing technology in medical practice became an attainable – and perhaps inevitable – future reality. To the extent that our medical destiny is imprinted on our genes, genetic testing has the potential to facilitate unprecedented prediction, diagnosis, and treatment of disease. The emergence of such new possibilities has raised widespread concerns about genetic privacy and discrimination, informed consent, and lack of sufficient regulation, particularly in relation to genetic tests that are designed to predict future disease. Federal regulation of genetic testing is currently incomplete – the FDA and other related agencies have yet to provide adequate regulatory oversight for the growing genetic testing field.

This article argues that an excessive focus on the admittedly serious ethical and policy implications of predictive genetic testing by government agencies, expert panels, legal academia, and the public has impeded recognition of the significance of pharmacogenomics, a form of genetic testing that promises to bring about widespread and revolutionary changes to routine medical care. Federal agencies that regulate laboratory testing and medical devices, most crucially the FDA, must focus on preparing the medical system for the future central role of pharmacogenomics in the process of testing, prescription, and delivery of drugs.

Part I of this article provides an overview of genetic testing generally and pharmacogenomics in particular.

Part II lays out the current state of federal regulation of genetic testing. Part III describes recent attempts, largely through government sponsored advisory groups, to improve federal oversight of genetic testing. Part IV suggests that although the advice put forth by such advisory groups and by legal academics is important, it is excessively focused on preventive genetic testing and places insufficient emphasis on pharmacogenomic genetic testing.

Part I: Genetic Testing and Pharmacogenomics

Genetic testing involves the analysis of DNA, RNA, chromosomes, or certain gene products to detect heritable, disease-related DNA alterations.¹ Genetics-based molecular testing has been available for approximately a decade,² and can currently be used to test for over 900 diseases, including disorders as disparate as Alzheimer's disease and colorectal cancer.³ The number of genetic tests performed is expected to continue to increase dramatically each year.⁴

Genetic testing may be used for a variety of purposes. Diagnostic testing confirms or rules out a particular diagnosis in a symptomatic patient; predictive testing determines whether a relevant genetic mutation is present in an asymptomatic individual; carrier testing determines whether an asymptomatic individual carries a particular recessive genetic mutation; prenatal testing is used during pregnancy to determine the health of the fetus; pre-implantation testing is used to test embryos produced through in vitro fertilization,

¹Task Force on Genetic Testing, Nat'l Inst. Of Health – Dept. of Energy, Final Report: Promoting Safe and Effective Genetic Testing in the United States (Sept. 1997), available at <http://www.nhgri.nih.gov/ELSI/TFGT_final/index.html> [hereinafter "Task Force Report"].

²Cindy Coty, *Delays on the Road to Genetic-Based Testing; Why So Many Diagnostic Tests Have Stalled in the Lab En Route to the Medical Clinic*, Genomics and Proteonomics at 51 (Oct. 1, 2002).

³Genetests (a genetics information resource funded by NIH, HRSA and DOE), available at <<http://www.genetests.org>> (last visited February 20, 2003). [hereinafter "Genetests"]; Anny Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 Food & Drug L. J. 555, 558 (1998).

⁴*GartnerG2 Says Physicians Should Prepare to Partner with Genetic Consultants as Genetic Testing Begins to Emerge*, Business Wire (June 18, 2002).

to reduce the risk of the fetus having a particular genetic condition; and newborn screening is performed routinely at birth, often mandated by the state.⁵

Each use raises distinct practical, legal and ethical issues. The most controversial use and that which has generated the most literature, however, is predictive testing. Critics contend that predictive testing may be unreliable, and they point to the lack of treatment for many diagnosed diseases for which genetic testing is or will soon be possible, as well as to the potential for genetic discrimination.

Genetic mutations are the cause of about 3000 to 4000 disorders, and some of these, including Huntington's disease, sickle-cell anemia, and cystic fibrosis, are linked to mutations in a single gene.⁶ For many such diseases, genetic diagnosis is now common, but finding or failing to find a disease-related genetic variation is not always conclusive, because some genetic variations in disease-related genes may be benign. The gene linked to cystic fibrosis, for example, can contain any of over 300 different mutations – some of these do not appear to be related to disease, while others are linked to varying degrees of disease.⁷ In such cases, a positive genetic test does not necessarily mean that the subject will develop the disease, while a negative test can be equally unclear, since the tests screen only for the most common mutations.⁸

Most diseases cannot be linked to a single gene, but are instead linked to a mix of causes that may include carcinogens, diet, environment, and genetic mutations. The relationship among these causes is not well-understood.⁹ Even when an inherited gene has caused numerous cases of disease within a family (as often occurs with breast-cancer related genetic mutations, for example), some carriers may remain healthy, perhaps due to lack of some environmental factor – genes may, for example, be switched on by sunlight.¹⁰ The result

⁵Genetests, *supra* note 3.

⁶Notices, Department Of Health And Human Services, Secretary's Advisory Committee on Genetic Testing, 64 Federal Register 67273, 67275 (Dec. 1, 1999).

⁷Access Excellence at the National Health Museum Resource Center, *Understanding Gene Testing; What are the limitations of gene testing?* Available at <<http://www.accessexcellence.org/AE/AEPC/NIH/gene19.html>> (last visited February 21, 2003) [hereinafter "Access Excellence"].

⁸Access Excellence, *supra* note 7.

⁹Notices, 64 Federal Register at 67275, *supra* note 6.

¹⁰Access Excellence, *supra* note 7.

of such uncertainty is that genetic testing cannot reliably predict future disease or the lack of it. Those receiving the results of a genetic test may not learn of or understand the probabilities associated with the data, and may either take drastic preventive steps or become dangerously complacent about their chances of developing a disease. The risk of inadequate consumer information has become especially great with the advent of direct-to-consumer advertisements for genetic testing, which often inaccurately imply that particular genetic tests will produce conclusive results.¹¹

Genetic testing for incurable diseases raises particularly troubling questions. When a genetic test for an incurable disease cannot provide a conclusive result, individuals who test positive for a relevant mutation must deal with perhaps unwarranted fear. In the case of incurable diseases that may be diagnosed conclusively through genetic testing (such as Huntington's disease), those at risk must decide whether they want to know if they carry the gene, and once they find out, they may live many healthy years fearing their future decline. The specter of widespread predictive testing of this kind has led many to call for significant expansion of genetic counseling services and concerted study of the ethical implications of such testing.¹²

Discrimination in insurance, employment and other contexts is another danger associated with predictive genetic testing. Instances of such discrimination have already been reported,¹³ and promise to become more common as researchers learn more about genetic links to disease and become better at predicting future disease long before symptoms appear. About half the states in the United States currently have some

¹¹One recent playbill advertisement for a BRCA breast cancer predictive genetic test, for example, showed a woman covering her breast, and stated "There is no stronger antidote for fear than information." It also stated that information "could provide hope. And dispel fear." Sandra Gollust, Sara Hull, Benjamin Wilfond, *Limitations of Direct-to-Consumer Advertising for Clinical Genetic Testing*, 288 JAMA 1762, 1763 (2002).

¹²See, e.g., Task Force Report, *supra* note 1; NIH Report, *Enhancing the Oversight of Genetic Tests: Recommendations of the SAGT* (2000) [Hereinafter "SAGT Report"].

¹³See, e.g., Jennifer Krumm, *Genetic Discrimination: Why Congress Must Ban Genetic Testing in the Workplace*, 23 J. Legal Med. 491, 492 (2002) (describing recent cases of genetic discrimination, including one in which a man was refused a government job because his brother had Gaucher's disease, and another in which a woman was fired after she disclosed that she was at risk for developing Huntington's disease.)

legislation prohibiting genetic discrimination in the workplace,¹⁴ and the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA) prohibits the use of genetic information without a diagnosis of the actual condition.¹⁵ Many commentators find these protections weak and under-inclusive, however, and call for much more expansive legislation to prevent discrimination on the basis of genetic information.¹⁶

Pharmacogenetics and Pharmacogenomics

“Pharmacogenetics” is the study of how genetic differences among individuals correspond to variability in drug response. Researchers track such differences by identifying “single nucleotide polymorphisms” (SNPs), single base pair alterations in the normal human genetic sequence found in small percentages of the population.¹⁷ (Variant genetic sequences are labeled “polymorphisms” if they are found in more than one percent of the population).¹⁸ These variations, especially those affecting pharmacokinetics (drug absorption, distribution, metabolism, and excretion), can significantly alter drug effectiveness or increase side effects in individuals carrying them.¹⁹ Detailed pharmacogenetic research has been advanced by the recent development of DNA chips – silicon chips embedded with large numbers of distinct bits of DNA. DNA chips could allow large-scale screening to be performed quickly, either to search for thousands of SNPs in one individual’s genes, or to study the gene expression of thousands of individuals who share a particular disorder, in order to determine whether they share a particular SNP.²⁰ There is evidence, for example, that some of the variant

¹⁴Robert Curley, Jr. & Lisa Caperna, *The Brave New World is Here: Privacy Issues and the Human Genome Project*, 70 Def. Couns. J. 22, 32 (2003).

¹⁵Curley & Caperna, *supra* note 14, at 29.

¹⁶See, e.g., Curley & Caperna, *supra* note 14; Krumm, *supra* note 13; Michael Stein & Anita Silvers, *An Equality Paradigm for Preventing Genetic Discrimination*, 55 V. and L. Rev. 1341 (2002); Jared Feldman & Richard Katz, *Genetic Testing & Discrimination in Employment: Recommending A Uniform Statutory Approach*, 19 Hofstra Lab. & Emp. L.J. 389 (2002); Jennifer R. Taylor, *Mixing the Gene Pool and the Labor Pool: Protecting Workers from Genetic Discrimination in Employment*, 20 Temp. Envtl. L. & Tech. J. 51 (2001).

¹⁷Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients’ Genetic Profiles*, 43 Jurimetrics J. 1, 6 (2002).

¹⁸Noah, *supra* note 17, at 6.

¹⁹Noah, *supra* note 17, at 3.

²⁰Michael Malinowski, *Law, Policy, and Market Implications of Genetic Profiling in Drug Development*, 2 Hous. J. Health L. & Pol’y 31, 40 (2002) (hereinafter “Malinowski I”).

alleles linked to adverse drug reactions are associated with certain ethnic groups,²¹ and such experiments can illuminate these types of connections.

The knowledge about individualized drug response that such new technology will bring promises to lead to a new, potentially significant use of genetic testing. Labeled “pharmacogenomics,” it involves using genetic information to customize medical treatment to a person’s particular genetic makeup.²² Today’s medicines are marketed as “one-size-fits-all” for any particular medical problem, despite the fact that individuals can differ dramatically in their responses to a drug treatment. Variability based on dosage responses, allergic reactions, and other often hereditary factors leads to side effects that kill 100,000 Americans a year, make 2 million others seriously ill,²³ and, some estimate, lead to health care costs of up to \$100 billion annually.²⁴ Although it is unlikely that tracking SNPs will completely eliminate adverse drug reactions, pharmacogenomics promises an enormous improvement over the current system, under which doctors guess proper dosages or drug choice based on generalized adverse reaction and dosage data, and then alter the prescription based on observable patient reaction. The danger of the current trial-and-error system is particularly great for children, women, and minority groups, since clinical trials that provide data on side effects and dosage are usually performed on a sample made up mostly of adult white males, a problem that the FDA has begun to respond to only in the last decade.²⁵ The danger is also great for America’s elderly, who are reaching ages not reached by previous generations and thus untested as to dosage and drug reaction.²⁶ Within five years, tailored prescriptions may begin to significantly diminish such problems, and it may become commonplace for doctors to rely on genetic testing to aid dosage or drug prescription decisions.²⁷

²¹Lars Noah, *supra* note 17, at 9.

²²Lars Noah, *supra* note 17, at 3.

²³Rick Weiss, *The Promise of Precision Prescriptions; ‘Pharmacogenomics’ Also Raises Issues of Race, Privacy*, Wash. Post A01 (June 24, 2000) (hereinafter “Weiss I”).

²⁴Malinowski I, *supra* note 20, at 39.

²⁵Lars Noah, *supra* note 17, at 12-13.

²⁶Malinowski I, *supra* note 20, at 39.

²⁷Weiss I, *supra* note 23.

Interest in pharmacogenomics has also led to the development of a new field, nutritional genomics (or “nutrigenomics”), which may ultimately prove as far-reaching and significant as pharmacogenomics. Nutrigenomics studies the genetic element of the relationship of food to health, analyzing generally how particular foods affect health, and more specifically how genetic makeup affects the way that individuals react to foods. There may, for example, be genetic reasons that the same food raises blood pressure in one individual but has no such effect on another. Ultimately, nutrigenomics may allow diet to be tailored to an individual’s genetic makeup, so that different varieties of mass market products can be geared to particular subpopulations – say, to people with hereditary slow metabolism, or hereditary potential for high cholesterol.²⁸

Both pharmacogenomics and nutrigenomics promise to affect a revolution in medical treatment. The most significant result may be the routinization of genetic testing – once pharmacogenomic and nutrigenomic methods become widespread, genetic testing will become necessary to obtain a prescription or to be a knowledgeable food consumer, and will thus move from its peripheral role in the current medical establishment to a central one. The ramifications of such a change are discussed below.

Part II: Government Regulation of Genetic Testing

Three criteria are generally considered relevant for identifying reliable diagnostic tests: analytical validity, clinical validity, and clinical utility.²⁹ Analytical validity refers to whether a test properly measures the property it is designed to measure; an analytically valid genetic test produces a positive result when the relevant genetic mutation is present (it thus has “analytical sensitivity”) and a negative result when it is

²⁸See generally Andrew Pollack, *New Era of Consumer Genetics Raises Hope and Concerns*, N.Y. Times F5 (Oct. 1, 2002).

²⁹See, e.g., SACGT Report, *supra* note 12, at 15-17; Michael Malinowski & Robin Blatt, *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 Tul. L. Rev. 1211 (1997) (hereinafter “Malinowski & Blatt”).

not (it thus has “analytical specificity”).³⁰ Clinical validity relates to the predictive value of the test in a clinical setting – in other words, whether and to what degree a positive result is indicative of a medical condition.³¹ Finally, clinical utility is an indicator of whether the test is in fact clinically useful, in the sense that increasing its use would positively affect treatment outcomes.³² As described below, most genetic tests are currently monitored only for analytical validity, although a small number are tested for clinical validity and utility as well.

The FDA has authority to regulate genetic testing technology. Genetic tests are considered “diagnostic” and are thus medical devices under the Federal Food, Drug, and Cosmetics Act’s 1976 Medical Devices Amendment (MDA), which grants the FDA authority over, among other things, “in vitro reagent[s], or any other similar or related article, including any component, part, or accessory, which is... intended for use in diagnosis of disease or other conditions... .” 21 U.S.C.A. § 321(h). The MDA separates medical devices into three classes regulated in differing degrees based on the concerns they raise about safety and effectiveness. 21 U.S.C.A. § 360c(a). Although the laboratory procedures required for genetic testing are relatively simple, most genetic tests are considered Class III devices due to the complexity of the criteria for determining their effectiveness.³³ Class III genetic tests must undergo pre-market approval, a process that requires developers to submit data to the FDA on their test’s safety and effectiveness before they can offer it for sale, unless they can demonstrate “substantial equivalence” to a previously approved device.³⁴ This rigorous inspection involves testing for analytical validity, as well as clinical validity and clinical utility.³⁵

³⁰SACGT Report, *supra* note 12, at 15.

³¹*Model Act for Genetic Privacy and Control*, 88 Iowa L. Rev. 121, 128 (2002).

³²SACGT Report, *supra* note 12, at 16-17.

³³Jennifer S. Geetter, *Coding for Change: The Power of the Human Genome to Transform the American Health Insurance System*, 28 Am. J.L. & Med. 1, 31(2002).

³⁴Huang, *supra* note 3, at 588.

³⁵Note, Allen C. Nunnally, *Commercialized Genetic Testing: The Role of Corporate Biotechnology in the New Genetic Age*,

Although the MDA classification system appears to require significant FDA regulatory oversight of genetic testing, in reality most genetic testing is only minimally scrutinized due to a regulatory loophole that genetic testing companies have been quick to use to their advantage. Genetic tests can be offered in two forms. In the first, the test is sold directly to hospitals, laboratories, or other health practitioners as “kits,” which are regulated as Class III devices. Companies can, however, offer to test the samples in their own laboratories; in that case, the doctor sends the company a DNA sample, and the company sends back the results – this is typically called a “home brew.” The FDA considers home brews to be “services,” and thus not within the MDA regulatory requirements.³⁶ Thus, many genetic tests identical to “kits” escape the Class III pre-market approval process entirely.

Companies offering home brew genetic testing are not, however, entirely free from oversight. Like all laboratories offering tests for clinical purposes (approximately 175,000 in the United States³⁷), these companies are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which is administered by the Centers for Medicare and Medicaid Services (CMS) in partnership with the Centers for Disease Control (CDC). CLIA requires that every laboratory demonstrate the analytical validity of its tests before offering them as a service to the public, meaning in essence that the laboratory must demonstrate its technical competence.³⁸ CLIA does not, however, require demonstration of either clinical validity or clinical utility.³⁹ In other words, although home brew genetic tests must accurately identify the genetic property they test for, this property need not be clinically significant. Entirely free from oversight in this regard, companies

8 B.U. J. Sci. & Tech. L. 306, 335 (2002).

³⁶Geetter, *supra* note 33, at 34.

³⁷See Centers for Medicare and Medicaid Services, <<http://www.cms.hhs.gov/clia/>> (last visited February 22, 2003).

³⁸Neil Holtzman, *Symposium, Legal Liabilities at the Frontier of Genetic Testing, Part I. FDA and the Regulation of Genetic Tests*, 41 *Jurimetrics J.* 53 (2000).

³⁹Nunnally, *supra* note 35 at 335.

can easily exaggerate the importance of their results. Several commentators have noted that CMS personnel administering CLIA have neither the time nor the training to test for clinical validity or clinical utility, and argue that as a result, any move to broaden such regulation would likely have to be initiated outside of CLIA.⁴⁰

Even on a basic accuracy level, CLIA is considered insufficient by many to regulate genetic testing, in part because its requirements are not specifically designed for genetic testing,⁴¹ and in part because its scope of regulation is so wide that details can easily be missed. As one commentator has stated, “CLIA is marred by reporting deficiencies and laboratory inspections that are infrequent and insufficient.”⁴² In one early 1990s study, the federal government found that 80 to 84 percent of the general physician office labs inspected had problems under CLIA, and eleven percent had serious problems.⁴³ Another study of 245 molecular genetic testing labs by a group of geneticists at New York’s Mt. Sinai School of Medicine found that 15 percent of the labs – all under CLIA oversight – scored lower than 70 percent on a quality control test.⁴⁴ Overall, a “general lack of regulatory quality control on genetic tests . . . raises questions about their fundamental reliability.”⁴⁵ Many commentators argue that the FDA should have a central role in regulating both genetic testing kits and “home brews,” based on the agency’s technical competence, experience, and proven record regulating genetic tests.⁴⁶

Although the FDA does not regulate home brews, it asserts authority to do so; the agency has said that it

⁴⁰Holtzman, *supra* note 38 at 57.

⁴¹*See, e.g.* Task Force Report, *supra* note 1; Huang, *supra* note 3, at 590; Lori Andrews, *A Conceptual Framework for Genetic Policy: Comparing the Medical, Public Health, and Fundamental Rights Models*, 79 Wash. U. L.Q. 221, 257 (2001).

⁴²*See, e.g.*, Michael J. Malinowski, *Legal Liabilities at the Frontier of Genetic Testing, Part I. Separating Predictive Genetic Testing From Snake Oil: Regulation, Liabilities, And Lost Opportunities*, 41 *Jurimetrics J.* 23, 42 (2000) (hereinafter “Malinowski II”) (“CLIA alone is unreliable even as a laboratory quality assurance measure.”); Andrews, *supra* note 41 at 257.

⁴³*See* Andrews, *supra* note 41 at 257.

⁴⁴*See* Judy Peres, *Genetic Testing Can Save Lives – But Errors Leave Scars*, *Chic. Trib. C1* (Sept. 26, 1999).

⁴⁵Malinowski & Blatt, *supra* note 29, at 1233.

⁴⁶*See, e.g.*, Malinowski II, *supra* note 42, at 43; Huang, *supra* note 3, at 590.

lacks the resources to engage in such extensive regulation.⁴⁷ Some critics have suggested that the FDA is cautious about regulating genetic technology generally, due to the unique ethical ramifications and practical challenges associated with the subject matter and the heated political controversies surrounding it.⁴⁸ The agency may also be skittish after much criticism over its previous attempts to impede market entry of testing technologies, including home HIV test kits and home drug test kits.⁴⁹

Part III: The Controversy Over Reform

Regardless of the reasons for the FDA's reluctance to impose uniform regulatory requirements on all genetic testing technology, the discrepancy between the agency's strict oversight of test kits and its complete lack of oversight of home brews has generated calls for change for years.⁵⁰ On the other hand, the biotechnology industry has met such recommendations for reform with concerns about the effects increased regulation would have on the development and profitability of genetic testing.⁵¹

This controversy, as well as a more general concern that genetic technology was improving at a rate faster than law was changing to accommodate it, led in 1997 to the establishment of a "Task Force on Genetic Testing," sponsored by the National Institutes of Health (NIH) and the Department of Energy (DOE) and composed mostly of academics and doctors. The Task Force's goal was to "review genetic testing in the

⁴⁷The FDA has indicated that while [c]urrently, FDA is not regulating testing[,] the agency maintains that it has such authority but lacks the resources to review the technology or make and enforce new regulations for the field. F-D-C Reports, Inc., *OncorMed BRCA1 Testing Service Commercialization Enters Second Phase Through New IRB Protocol*, The Blue Sheet, (Jan. 17, 1996); *See also* SACGT Report, *supra* note 12, at 10 ("FDA has stated that it has authority, by law, to regulate such tests, but the agency has elected as a matter of enforcement discretion to not exercise that authority, in part because the number of such tests is estimated to exceed the agency's current review capacity.").

⁴⁸*See, e.g.* Geetter, *supra* note 34, at 32-33; Huang, *supra* note 3, at 571.

⁴⁹Huang, *supra* note 3, at 571-2.

⁵⁰*See, e.g.*, Malinowski & Blatt, *supra* note 29; Malinowski II, *supra* note 42; Holtzman, *supra* note 38; Huang, *supra* note 3; *but see* Richard Merrill, *Symposium: Legal Liabilities at the Frontier of Genetic Testing. Genetic Testing: A Role for FDA?*, 41 *Jurimetrics J.* 63 (2000), arguing that the home brew/test kit distinction may be justified based on jurisdictional concerns, lack of FDA expertise, and budgetary limitations.

⁵¹*See* SACGT Report, *supra* note 12, at 26.

United States and make recommendations to ensure the development of safe and effective genetic tests.”⁵² In September of 1997, the Task Force released a detailed final report entitled “Promoting Safe and Effective Genetic Testing in the United States,” in which it expressed the general view that commercialization of genetic testing was advancing too quickly without sufficient legal safeguards. It recommended a focus on preventing discrimination and on access to information through patient informed consent, education of health professionals, and widely-available genetic counseling.⁵³ The Task Force also recommended eliminating the distinction between genetic testing kits and home brews, but did not specify what role the FDA should play in this new regulatory structure.⁵⁴

In 1998, partially in response to the Task Force’s recommendations, then-Secretary of Health and Human Services Donna Shalala chartered the Secretary’s Advisory Committee on Genetic Testing (SACGT).⁵⁵ The SACGT, managed by the NIH, had a mandate to “advise the government about all aspects of the development and use of genetic tests, including the complex medical, ethical, legal, and social issues raised by genetic testing.”⁵⁶ SACGT gathered information, including public commentary, in 1999 and 2000, and released a final report in July 2000 – “Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT.”⁵⁷ In the report, SACGT concluded that “the FDA should be the federal agency responsible for the review, approval, and labeling of all new genetic tests that have moved beyond the basic research phase,” thus disapproving, as the Task Force had, of the current two-pronged genetic testing regulatory system.⁵⁸ The Committee recommended pre-market review of all genetic tests for analytical validity, clinical validity, and

⁵²Task Force Report, *supra* note 1.

⁵³Task Force Report, *supra* note 1; William Allen, *Panel Seeks Safeguards for Genetic Tests; Expanding Technology Worries Group*, St. Louis Post-Dispatch 9A (October 24, 1997).

⁵⁴See Huang, *supra* note 3, at 555.

⁵⁵See “About Secretary’s Advisory Committee on Genetic Testing,” available at <<http://www4.od.nih.gov/oba/sacgt.htm>> (last visited February 28, 2003) [hereinafter “SACGT website”].

⁵⁶See SACGT website, *supra* note 55.

⁵⁷See Nunnally, *supra* note 35, at 335-6.

⁵⁸See SACGT Report, *supra* note 12, at 27.

clinical utility, and advised that this review include a consideration of social consequences as well. It suggested that the stringency of regulation should vary for different genetic tests, based on a categorization system that might take into account criteria such as “test characteristics, availability of safe and effective treatments, and the social consequences of a diagnosis or identification of risk status.”⁵⁹ In the report, the Committee promised to release an addendum describing such a categorization system shortly.⁶⁰ When the Addendum was released in September 2001, however, it instead described a process of exploring several possible categorization systems but agreeing on none, due to perceived under- or over-inclusiveness of the various proposals.⁶¹ The report stated:

After consideration of the public comments and additional discussion, the Committee concluded that fundamental, irresolvable questions had been raised about the feasibility of categorizing tests for oversight purposes based on a limited set of elements in a simple, linear fashion.⁶²

The biotechnology industry responded to SACGT’s recommendations with apprehension. As reported by the SACGT, “a number of individuals from industry and professional organizations expressed concerns about the impact that additional oversight may have on the development, availability, and accessibility of genetic tests and expressed strong opposition to an increased role for FDA.”⁶³ On the other hand, earlier empirical data had indicated that some members of the genetic testing industry favored FDA regulation to improve testing reliability; one 1995 study found that a majority of companies surveyed (including organizations involved in genetic testing or a related field) agreed that “FDA policies, or lack of policies, hinder the development of

⁵⁹See SACGT Report, *supra* note 12, at 21.

⁶⁰See SACGT Report, *supra* note 12, at 23.

⁶¹See *Development of a Classification Methodology for Genetic Tests: Conclusions and Recommendations of the Secretary’s Advisory Committee on Genetic Testing*, available at <http://www4.od.nih.gov/oba/sacgt/reports/Addendum_final.pdf> (last visited February 28, 2003) [hereinafter “SACGT Addendum”].

⁶³SACGT Report, *supra* note 12, at 26; *see also* Nunnally, *supra* note 35, at 336.

safe and effective genetic test kits or other products.” A vast majority found that “[s]ome laboratories that offer genetic testing lack quality assurance programs,” and only a small number agreed with the statement that CLIA policies “assure the quality of genetic test services.”⁶⁴

By 2001, FDA reform of its bifurcated genetic testing regulation system was widely thought to be imminent.⁶⁵ The FDA was feeling pressure both from academic commentators and from expert panels to initiate reform, and several steps undertaken by the Department of Health and Human Services and the FDA itself appeared to move in this direction. In a January 19, 2001 letter to the SACGT in response to its report, Secretary of Health and Human Services Donna Shalala outlined a new oversight plan for genetic testing, which, she wrote, would be particularly responsive to SACGT’s recommendation that “FDA should be the federal agency responsible for the review, approval and labeling of all new genetic tests that have moved beyond the basic research phase.” Under the program, she wrote, “oversight of genetic tests will cover clinical genetic testing services (so called ‘home brews’) as well as genetic test kits.”⁶⁶ In the SACGT addendum, the Committee commented on this progress, and cited the planned changes as an additional reason that SACGT work had temporarily ceased:

SACGT’s decision to defer further work was also based on significant progress made by FDA to develop an innovative regulatory process for genetic tests. At its February 2001 meeting, SACGT was briefed about the agency’s plans for pre-market review of genetic tests.⁶⁷

The FDA’s plans never came to fruition, however – the effort slowed significantly after the transition from the Clinton to the Bush administration, and in September 2002, the new Health and Human Services Secretary, Tommy Thompson, disbanded the SACGT, replacing it with the newly formed Secretary’s Advisory

⁶⁴ See Task Force Report, *supra* note 1, at Appendix 3; see also Andrews, *supra* note 41, at 256.

⁶⁵ See, e.g., Nunnally, *supra* note 35, at 337 (“Recommendations recently made by the [SACGT] indicate that diagnostic genetic testing will soon fall within the purview of FDA regulation.”; SACGT Addendum, *supra* note 61, at 7.

⁶⁶ Letter from Donna Shalala, Secretary of Health and Human Services, to Edward McCabe, Chair of the SACGT, on January 19, 2001, available at <<http://www4.od.nih.gov/oba/sacgt/McCabe.pdf>> (last visited March 12, 2003).

Committee on Genetics, Health, and Society (SACGHS). The SACGHS has yet to schedule any meetings or release any substantive documents.⁶⁸ This change was met with widespread consternation, particularly as it was part of a substantial reshuffling of those scientific advisory groups perceived to be out of line with the administration's thinking.⁶⁹ As one commentator has noted, while every administration tends to appoint new committee members,

[w]here this administration is breaking with tradition is in its apparent lack of concern about how this process is viewed by the broader scientific community and its seating of lobbyists and political operatives on such committees.⁷⁰

The change was thus viewed by many as a political maneuver founded on the administration's disagreements with the SACGT and its desire to appease the biotechnology industry, although the administration insisted that it had no such intention, arguing that such an overhaul is normal during the first year of an administration.⁷¹

Part IV: A Mistaken Approach

In light of the nearly unanimous consensus among experts that current FDA regulation of genetic testing services is insufficient and improperly structured, the Bush administration's sudden elimination of the SACGT and consequent delay of FDA reform was a mistake, and is likely to delay much-needed progress by many years. Had the FDA initiated the expected changes, however, some of the most significant problems with the current system would not have been addressed regardless. Any real attempt to meet the coming genetic testing revolution requires recognition of the new role that such testing will soon play in medical treatment through pharmacogenomics, a fact that neither the government advisory groups nor academic commentators

⁶⁸See "Secretary's Advisory Committee on Genetics, Health, and Society, available at <<http://www4.od.nih.gov/oba/sacghs.htm>> (last visited March 6, 2003).

⁶⁹See, e.g., Rick Weiss, *HHS Seeks Science Advice to Match Bush Views*, Wash. Post A01 (Sept. 17, 2002) (hereinafter "Weiss II") ("The Bush administration has begun a broad restructuring of the scientific advisory committees that guide federal policy in areas such as patients' rights and public health, eliminating some committees that were coming to conclusions at odds with the president's views and in other cases replacing members with handpicked choices."); Jon Carroll, *Iraq! Iraq! Pay No Attention To Other Things!* San Fran. Chronicle D12 (Sept. 26, 2002); Kathi E.Hanna, *Whose Advice? Expert Committees Get a Makeover; Capital Report*, 32 The Hastings Center Report 13 (November 1, 2002).

⁷¹See Weiss II, *supra* note 69.

have fully appreciated.

As of today, genetic testing is a largely peripheral issue for the general public. Genetic testing captures the public imagination due to its potential predictive power and concomitant ethical ramifications, as well as its popular association with even more controversial scientific advances such as stem cell research and human cloning. The reality of receiving a genetic test as part of medical treatment, however, is foreign to the vast majority to Americans.

This will soon change. Although predictive testing is the most well-known type of genetic testing today, it will never, by its nature, impact more than a small percentage of the population. Even as scientific understanding of genetic links to disease grow, there will remain only a relatively small number of diseases that can be predicted to a certainty through genetic testing, and many disorders will remain sufficiently unpredictable that a test would be medically uninformative. Pharmacogenomics, on the other hand, is likely to become universal once it advances far enough to provide reliable information. Many researchers predict that pharmacogenetic research will lead to the categorization of diseases by genetic trait rather than by type or body part: there won't be stomach or breast cancer, but rather cancer with a particular genetic characteristic, treated with a drug particularly manufactured for that genetically identified cancer.⁷² Under such a system, genetic testing will become a required part of disease diagnosis and drug prescription, since it will be the only method for determining the unique genetic profile of a particular individual's disease, and tailoring a drug to fit that profile. As one commentator has noted, "genetic testing is entering the medical setting as an accompaniment to drug delivery."⁷³ The social and legal ramifications of such a change are unfathomable.⁷⁴ The FDA should now view genetic testing not as a distinct diagnostic procedure for which regulatory funding can be cut when money is tight, but as a part of medical care as critical to patient safety

⁷²See Sharon Begley, *Made to Order Medicine*, Newsweek 64 (June 25, 2001).

⁷³Malinowski I, *supra* note 20.

⁷⁴See Weiss I, *supra* note 23.

as any drug that the FDA regulates.

Recognition of this change in the role of genetic testing in medicine must accompany any reform in genetic testing regulation. The current discussion of genetic testing remains, however, mired in an outdated understanding of the real importance of such testing. How should the FDA adapt as the sheer number of genetic tests performed in the United States skyrockets, and genetic tests become routine? Neither the expert panels that have considered genetic testing nor the academics that study its legal implications have seriously considered this question.

Expert Panels

Although the mandate of the Task Force on Genetic Testing was very general – “to review genetic testing in the United States and make recommendations to ensure the development of safe and effective genetic tests” – its report stated clearly that it was “primarily concerned about predictive uses of genetic tests,”⁷⁵ implying that predictive tests present the most significant policy questions and require the most expert attention. Thus, the report emphasized improved regulation of test accuracy generally, but focused on the many ethical issues that arise in the predictive testing arena specifically. In stating its “overarching principles,” the Task Force listed concerns such as informed consent (“It is unacceptable to coerce or intimidate individuals or families regarding their decision about predictive genetic testing.”), the ethics of testing children for adult-onset diseases, confidentiality, and discrimination. The report makes no mention of pharmacogenomics, or of the implications of non-predictive genetic testing in general.⁷⁶

The SACGT, which had a comparably broad mandate to “advise the Department of Health and Human Services (DHHS) on the medical, scientific, ethical, legal, and social issues raised by the development and

⁷⁵Task Force Report, *supra* note 1.

⁷⁶*See* Task Force Report, *supra* note 1.

use of genetic tests,”⁷⁷ similarly focused on predictive genetic tests because “their potential psychological, social and economic harm are so significant and the potential misuse of such information is so great.”⁷⁸ Like the Task Force, SACGT placed great emphasis on the need to improve regulation of genetic testing, but also on informed consent, genetic counseling and education, and discrimination in employment and health insurance, all most closely related to predictive genetic testing. The “Background” section of the Report mentions pharmacogenetics, stating that

Pharmacogenetic tests will provide information about the safety and effectiveness of drug therapies that will help health professionals determine how an individual is likely to respond to a medicine before it is prescribed, enabling beneficial drugs to be targeted and reducing drug reactions.⁷⁹

This is, however, the only section in which pharmacogenomics is mentioned, and pharmacogenomic genetic tests apparently do not figure into any further discussions of genetic testing in the report.

Legal Academia

The ethical and social implications of predictive genetic testing have been a fruitful topic for law review articles since such testing became a realistic possibility. A superficial search for “genetic testing” on any database of legal academic literature will bring up an enormous number of articles on genetic discrimination in employment and insurance,⁸⁰ a significant number on the ethics of disclosing genetic testing results for incurable diseases, either to the patient or to his or her relatives,⁸¹ but a miniscule number that discuss

⁷⁷SACGT Report, *supra* note 12, at vi.

⁷⁸SACGT Report, *supra* note 12, at 8.

⁸⁰*See, e.g.*, Curley & Caperna, *supra* note 14; Krumm, *supra* note 13; Thomas F. Wieder, *Privacy Protection is Needed for DNA*, 2002 L. Rev. Mich. St. U. Det. C.L. 927 (2002); Stein & Silvers, *supra* note 16.

⁸¹*See, e.g.*, Dianne E. Hoffman & Eric A. Wufsberg, *Testing Children for Genetic Predispositions: Is It in Their Best Interests?*, 23 J.L. Med. & Ethics 331 (1995); Eric T. Juengst, *The Ethics of Prediction: Genetic Risk and the Physician-Patient Relationship*, 1 Genome Sci. & Tech. 30 (1995); Angela Liang, *The Argument Against A Physician's Duty To Warn For Genetic Diseases: The Conflicts Created By Safer v. Estate Of Pack*, 1 J. Health Care L. & Pol'y (1998).

pharmacogenomics in any depth or mention genetic testing in a medical but non-predictive context.⁸² As of now, “genetic testing” appears to be synonymous with “predictive genetic testing” in the vast majority of legal literature on the subject, probably a reflection of the general public understanding of the terms.⁸³

The Need for a New Perspective

The implications of such a dearth of expert and academic legal commentary on the burgeoning field of pharmacogenomics are severe. The rise of pharmacogenomics promises to lead to a large number of legal, practical, and ethical questions, some of which have been raised by commentators in the context of predictive genetic testing, but others of which have not.

The biggest flaw in the current genetic testing regulatory system, and one which will become increasingly significant as pharmacogenomics gains in importance, is the lack of real regulation of genetic test reliability and accuracy. Both legal academics and the various expert panels that have considered the current system of regulation of genetic testing have called for reform in this area with commendable persistence. Their proposal that genetic tests, like drugs, be fully tested for analytical validity, clinical validity, and clinical utility before entering the market, and that the FDA regulate all genetic tests, regardless of their form, should be heeded.⁸⁴ Though the FDA’s expertise and jurisdiction to decide the many ethical dilemmas posed by predictive genetic testing is questionable, its ability and authority to regulate the reliability of

⁸²Among the few legal articles that discuss pharmacogenomics in any depth are: Noah, *supra* note 17; Malinowski I, *supra* note 20; Wendell W. Weber, *Rationales for Population-Specific Genetic Research: Pharmacogenetics in Indigenous Peoples*, 42 *Jurimetrics J.* 141 (2002); Carol Freund & Benjamin Wilfond, *Emerging Ethical Issues in Pharmacogenomics in Section 15: Posters and Multi-Media Presentations*, 29 *J.L. Med. & Ethics* 42, 46 (2001).

⁸³This of course excludes non-medicine related testing, such as genetic testing for forensic purposes.

⁸⁴*See, e.g.*, SACGT Report, *supra* note 12, at 15.

genetic testing is clear.

As pharmacogenomics leads to the routine use of genetic tests in conjunction with drug prescription, inaccuracy in a genetic test could become as life-threatening as a mistake in the drug composition itself; wrong results could lead to prescription of an inappropriate drug dosage, or of a drug that produces a severe adverse reaction. This is in stark contrast to predictive genetic tests, in which inaccurate test results may lead to counter-productive medical decisions in the long term, but do not present an immediate health risk. In this light, the FDA's previous unwillingness to reform the home brew/test kit regulatory dichotomy due to limited funds is incongruous, and the Bush administration's derailment of the SACGT's promising efforts to fix this system is unacceptable. A change of perspective is necessary: genetic tests are no longer peripheral medical devices secondary in importance to other products within the FDA's regulatory jurisdiction; they are as central as drugs themselves, and must be regulated as such.

Beyond general reliability, pharmacogenomic genetic testing raises other concerns for the FDA and other government regulatory agencies that have yet to be considered by experts and scholars, whose interest has been overly focused on predictive testing:⁸⁵

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⁸⁵For an excellent summary of many of the potential changes pharmacogenomics is likely to bring about, *see generally* Noah, *supra* note 17, the only article I have found that considers this question in depth.

Should genetic tests be sold “bundled” with particular drugs, or if not, should drug labels specify recommended genetic tests? Once drugs are marketed toward a particular genetic profile, these types of bundling systems will likely follow. Antitrust concerns may be raised by such arrangements.⁸⁶ In addition, genetic testing recommendations or requirements on drug labels would introduce a complex and significant new category of labeling language for the FDA to regulate. Inaccuracy in this regard could have dangerous health consequences.

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What if, as some experts predict, pharmaceutical companies target large genetically defined groups for a particular disease, and ignore smaller groups?⁸⁷ This phenomenon would be similar to the current “orphan drug” problem (which involves pharmaceutical companies failing to research drugs for rare diseases, due to a lack of potential profitability), but on a much larger scale. Such a practice might be particularly problematic as genetic differences often fall along racial and ethnic lines, leading to the possibility that fewer drugs for particular diseases will be available for certain minority groups.⁸⁸ Some genetically identified groups may also be labeled as generally “hard to treat” or “high risk subjects.”⁸⁹ How should such practices be regulated?

- Will subjects taking part in clinical tests required for FDA drug approval be required to take pharmacogenomic genetic tests? Such a change seems inevitable; as drugs are tailored to particular genetic characteristics, they will have to be tested on clinical subjects with the appropriate genetic profile. What changes should be made to accommodate this development? New privacy concerns for these test subjects will certainly arise.⁹⁰

⁹⁰Of course, this change will give rise to important benefits as well, even beyond those of pharmacogenomics generally. Using genetic testing with clinical trials will someday allow those who would have adverse reactions to be eliminated from the study before it begins, leading to much safer testing procedures. See Scott Brown in *The Proper Scope of IP Rights in the Post-Genomics Era: Symposium on Bioinformatics and Intellectual Property Law*, 8 B.U. J. Sci. & Tech. L. 233, 244-45 (2002).

- If genetic tests will be categorized into separate regulatory groups according to the needed stringency of oversight, as the SACGT originally suggested, how should this categorization be structured? The SACGT's view that "predictive tests require more scrutiny than diagnostic tests," and that "lower scrutiny would be needed for tests . . . used exclusively to direct clinical management of symptomatic patients"⁹¹ should be reconsidered in light of the factors mentioned in this article. While predictive testing may implicate certain ethical concerns to a higher degree than pharmacogenomic testing, the likely scope of future pharmacogenomic genetic testing and its medical importance argue for extremely strict regulation. The complexity of categorizing tests with such varied purposes will present a significant challenge for government regulators, the seriousness of which may not have been fully realized due to lack of consideration of pharmacogenomic genetic tests.

- More generally, pharmacogenomics is likely to greatly increase the complexity of the FDA's work in regulating prescription drugs and genetic tests. As drugs are customized, the number of drugs is likely to skyrocket, with each drug sold to much smaller populations. Stewarding such a large number of drugs through the approval system is likely to be a momentous task for the FDA, particularly with the added complexities of testing and labeling mentioned above. In addition, if genetic testing becomes a prerequisite of receiving a drug prescription, the universalization of genetic testing that will result could raise some of the same ethical and legal issues often discussed in the context of predictive testing, but on a much wider scale. For example, certain pharmacogenomic markers are likely to be associated with predictive and diagnostic genetic markers – in such cases, genetic discrimination and informed consent would be significant concerns.⁹²

Pharmacogenomics is a relatively new field, as yet adapted to clinical use only on a very small scale. It is perhaps to be expected that government agencies react to scientific changes as they arise and regulate based on the current state of affairs. Such a strategy is, however, inappropriate in the current genetic testing context, in which drastic and widespread changes are likely to occur in a very short time, a fact that the agencies themselves and the advisors and scholars who comment on their work have often failed to recognize. As one commentator has said: "The sooner that federal regulators, the courts, and other policymakers begin to appreciate the possibilities created by pharmacogenomic research, the more thoughtfully they can address the challenges presented by this exciting new technology."⁹³ The ethical quandaries presented by predictive genetic testing are certainly critical to resolve, but their philosophical appeal should not eclipse the practical

⁹¹SACGT Report, *supra* note 12, at viii.

⁹²Noah, *supra* note 17, at 22.

⁹³Noah, *supra* note 17, at 28.

and legal problems posed by pharmacogenomic research.