LAW, POLICY, AND MARKET IMPLICATIONS OF GENETIC PROFILING IN DRUG DEVELOPMENT

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INTRODUCTION

Completion of a map of the human genome¹ and the explosive emergence of a multitude of complementary technologies ranging from DNA chips (commonly referred to as "biochips")² to sophisticated software have transformed great expectations for genetic medicine into goals potentially obtainable in the foreseeable future.³

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² For a discussion of DNA chip technology and how it is accelerating drug development that is readily accessible to non-scientists, see CENTRE ROBBINS-BRUSS, FROM ACCOMPLISH TO IPO: THE BUSINESS OF BIOTECHNOLOGY 73-78, 225 tbl. B.1 (Persus Publishing, 2000).

³ For discussion of the range of enabling technologies being utilized for identification of genetic expression, see Michael J. Malinowski, Separating Pseudetic Genetic Testing From Snake Oil: Regulation, Liabilities, and Lost Opportunities, 41 J. OBJ. TECHNOL. 23, 31-33, 47 tbl. 1 (2000) [hereinafter Malinowski, Snake Oil]. See generally Arts Persists, Biotechnology in a Snapshot, 18 Nature Biotechnology 112 (2000) (Industry Trends Supplement). The technologies continue to evolve, and often in fundamental ways. For example, in March 2002, United States patent 6,355,420 was issued for a new methodology to sequence DNA that mimics nature's way of reading genetic information. See Teresa Riodan, Patents: An Obstacle with DNA and the Human Genome Leads to Development of a Technology, N.Y. Times,
The pharmaceutical and biotechnology industries are utilizing geneti-

cas-based research to improve decision-making and to streamline

drug development process, which has given rise to a field

known as pharmacogenomics. In simplest terms, pharmacogen-

omics is the study of the impact of genetic characteristics on the

health care of populations who share the characteristic(s) at issue.

Because of this approach to drug development, society should anticip-

ate the incremental market introduction of generations of drugs

with unprecedented genetic specificity and reduced side effects. These
drugs will be accompanied by heavy utilization of genetic profiling in

the delivery of health care. Moreover, genetic profiling will be

used increasingly to improve prescribing traditional pharmaceuticals,

and even to tailor some pharmaceuticals to accommodate

the genetic idiosyncrasies of individual patients. The study of

the impact of genetic characteristics on individual patients is a field

known as pharmacogenetics.

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Mar. 10, 2002, at C2 (profiling the work of Eugene Chan, founder and chairman of U.S.

Genomics).

1 Pharmacogenomics encompasses identifying cell function at the genetic level and using

predictable cellular response to chemical stimuli at the genetic level to drive drug develop-
mant. See Malinowski, Snake Oil, supra note 3, at 49 tbl. 2. This field is likely to accelerate.

2 See generally id. at 47 tbl. 1.

3 See Genetic Testing in the New Millennium: Advances, Standards, Implications Before the House

Subcommittee on Technology, 106th Cong., Apr. 21, 1999 (statement of Francis S. Collins); see also Malinowski, Snake Oil, supra note 3, at 31-33, 49 tbl. 2; see also Lever Hood & Lee

Malinowski, Snake Oil, supra note 3, at 31-33. 14

4 Malinowski, Snake Oil, supra note 3, at 31-33.

5 See Malinowski, Snake Oil, supra note 3, at 49 tbl. 2; see also Sharon Begley, Made-to-Order Medicine, Newsweek, June 25, 2001, at 65.

Utilization of pharmacogenomics and pharmacogenetics raise a multitude of law, policy, and market implications. These implications include:

1) A shift from decades of dependence on approximately 3,000 relatively crude pharmaceuticals that have been developed for 463 drug targets for the treatment of all human diseases to identification of between 3,000 and 10,000 drug targets for use in developing potentially tens of thousands of drugs; 10

2) Intense demand for human biological samples and access to pedigree and family histories; 11

3) Multiplication of the number of clinical trials and increased participation in trials; 12

4) More direct communication between human subjects, trial sponsors and investigators via Internet compilation and public dissemination of clinical trial information; 13

5) Increased commercial pressures on industry and collaborators in academia and medicine and, consequently, in the absence of regulatory reform, 14 raised risks to human subjects and research integrity; 15

6) Heightened medical privacy concerns as exponentially more genetic information will be obtained from individual samples; 16

7) Fracturing of traditional disease classifications and recognition of health conditions not yet fully identified; 27

8) Increased specificity in FDA drug labeling and restrictions on approved uses. 18
9) A surge in prescription drug prices and the intensity of coverage/reimbursement challenges resulting from allocation of higher research and development ("R&D") costs to smaller patient groups; 20

10) Pharmaceutical efforts to reach presently untapped markets, and to introduce preventive drug use to offset market losses attributable to the fracturing of traditional patient groups (resulting from division of tradition disease classifications) and increased prescription precision, which will introduce more new costs such as those associated with genetic screening; 20 and

11) Greater public and political support for price controls on pharmaceuticals because of a jolting rise in the prices of breakthrough new drugs and their delivery. 21

This article probes select law, policy, and market implications of utilization of genetic profiling in drug development and, consequentially, in the delivery of health care. Part I reflects upon traditional pharmaceuticals and the changing pharmaceutical economy. Part II identifies trends in pharmaceutical R&D with a focus on utilization of genetic profiling. Part III probes implications for the delivery of genetic profiling. Part IV probes implications for the delivery of health care and the roles of patients, research subjects, and providers, including pharmacists, and Part IV introduces proposals for responsive reforms.

I. TRADITIONAL PHARMACEUTICALS AND THE CHANGING PHARMACEUTICAL ECONOMY

After decades of solid profitability, pharmaceutical business plans to meet shareholder expectations based upon traditional rates of return have become uncertain if not wholly unrealistic. 22 Many of the industry's most profitable pharmaceuticals have gone off patent in recent years, and more key patents are approaching expiration. 23 Attempts by members of the pharmaceutical industry to extend market control over their products have become fodder for controversy and litigation. 24 Moreover, the generic drug industry has grown into a large, competitive, and increasingly influential sector, especially in an age of intense controversy over drug pricing. 25

Under the Hatch-Waxman Act, 26 generic competitors are able to enter the marketplace via an Abbreviated New Drug Application ("ANDA") by establishing bioequivalence 27 with approved products, rather than undertaking the more burdensome task of estab-

20. See Malinowski, FDA Regulation, supra note 20, at 224-25; see BOSTON CONSULTING GROUP, THE PHARMACEUTICAL INDUSTRY INTO ITS SECOND CENTURY: FROM SERENDIPITY TO STRATEGY 38-39 (1999). But see Virginia Murer Kahn, Managers Say this Decade Belongs to Health Care, N.Y. TIMES, Jan. 6, 2002, at 20 (arguing that more biotechnology companies are expected to post earnings in the next few years and the industry is still in a growth phase).

21. Notable examples of major revenue-generators that have gone off patent in recent years include Prilosec, AstraZeneca's drug to treat stomach ulcers, and Prozac, an antidepressant that generated extraordinary revenues for Eli Lilly. AstraZeneca has attempted to cushion its loss by introducing an allegedly improved version of Prilosec, Nexium, and Lilly now has a weekly version of Prozac. For identification of other pharmaceutical products losing patent protection from 2000 through 2003, including expiration date and sales information, see ROMEROS-ROTUI, supra note 2, at 164-165 tbl. 20.1.

22. For example, in December 2001, 29 attorneys general filed suit against Bristol-Myers Squibb to remove the company's market hold over Buspar, an anti-anxiety drug, so that generic drugs could enter the market. See Kahn, supra note 22, at 20. Prior to this action, the Federal Trade Commission, U.S. Attorney's Office in Boston, consumer coalition groups, and class action lawyers (including attorney veterans of the tobacco wars) filed various separate lawsuits against pharmaceutical makers. These suits were based upon allegations that the companies inflated drug prices, and often claimed that the defendants had been blocking the market introduction of generic versions of their medications. See Michael J. Malinowski, Health and Human Services, in DEVELOPMENTS IN ADMINISTRATIVE LAW AND REGULATORY PRACTICE 2000-2001 391-392 (Jeffrey S. Lubbers ed., ABA 2002).

23. See Generic Pharmaceutical Association (GPhA), at www.gpboonline.org (noting that while brand name prescription drugs represented 55% of all prescriptions, they consumed more than 50% of drug therapy dollars spent at retail).


25. "Bioequivalence" means equivalence in the amount of active drug that a product provides to the site of drug action. For more information, visit the FDA web site at www.fda.gov/ cder/ handbook/bioequiv.htm.
lishing fundamental safety and efficacy.28 Generic manufacturers thereby have the opportunity to enter the market without incurring hundreds of millions of dollars in R&D costs—for example, the costs associated with generating and processing often voluminous clinical data from Phase I through Phase III trials to establish safety and efficacy for market approval, and then follow-on studies and efficiency in the market development campaigns undertaken by drug innovators.29

Moreover, in spite of law reforms in favor of globalization of the life science markets such as enactment and implementation of the General Agreement on Tariffs and Trade ("GATT") and Trade-Related Intellectual Property Sections ("TRIPS"),30 longstanding seams among these global markets continue to unravel. Although the United States may remain optimistic about the promise of fully implementing GATT/TRIPS by 2015, even among signatories with developing economies, daunting challenges to global harmonization continue to arise.31 GATT/TRIPS is being implemented in the context of increasing disparity in life science capabilities among developed and developing economies, which is all the more difficult to ignore in an age of unprecedented global communication, international travel, and shared, increasingly ominous epidemiological challenges. The burgeoning biotech sectors of the United States and Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the market availability of drugs such as Herceptin for Europe and the 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intellectual property and inspired the government of South Africa, with the implied support of the World Trade Organization, to trump patent rights with public health overrides. The leading AIDS drug manufacturers within the pharmaceutical industry have made major concessions but have been unable to completely fend off generic competitors. Consequently, these nations have reaffirmed the pharmaceutical industry’s apprehensions about interacting with the governments of developing economies and widened over access to innovative pharmaceuticals and tensions over recognition of intellectual property rights. The absence of meaningful action by the World Trade Organization to develop areas of the life science capabilities in many biologically diverse areas of the world raises global susceptibility to public health challenges.

The pharmaceutical industry is responding to this plethora of challenges by changing its methodologies and dramatically increasing the percentage of revenue allocated to R&D. The overall revenue has grown from 11% to 18.5% over the last 20 years, and pharmaceutical investment in R&D has increased from $2 billion in 1991 to $30.5 billion in 2001.

Nevertheless, the pharmaceutical sector’s aggressive embrace of the precision in drug development introduced through biotechnology and fields such as pharmacogenomics will have major implications for cost-effectiveness in the United States. Thus, the cost to develop sequenced drugs for the multinational pharmaceutical behemoths whose sequences for these multinationals pharmaceutical behemoths whose sequences are premised upon volumetric scale and products exist is premised upon enormous scale and products exist, as noted in a recent report on the costs of pharmaceuticals.

II. Trends in Pharmaceutical R&D

Traditional pharmaceuticals are understood largely based upon use in human subjects and patients—meaning clinical trials and physician experiences that indicate which compounds alleviate and/or ameliorate symptoms associated with particular diseases. There is wide variation in patient responsiveness to most pharmaceuticals, ranging from non-responsiveness to severe adverse events from the standard of care dosage. Consequently:

1) Physicians have practiced broad off-label discretion, moving use of most pharmaceuticals well beyond the clinical trial design for efficacy and safety and resulting FDA labeling.

2) Our aging population now is testing the limits of our knowledge about drug combinations and interactions.


4) Estimates for the healthcare costs associated with unintended reactions to pharmaceuticals have reached as much as $100 billion annually, and

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38 Juma et al., supra note 31, at 630; Donald G. McNeil Jr., New List of Safe AIDS Drugs, N.Y. TIMES, Mar. 21, 2002, at A3 (“In a move that could help bring down the price of AIDS medicines for poor countries, the World Health Organization today released its first list of drugs for sale in safe AIDS drugs, which included a large Indian producer of generics manufacturers and three smaller European ones.”).


40 Cf. Juma et al., supra note 31, at 630; McNeil, supra note 39, at A3. For those who have not participated directly in dispute resolution with African nations over this issue of access, it may be presumptuous to declare that more information about these deliberations would be helpful.

41 See infra notes 151-154 and accompanying text.

42 See generally BOSTON CONSULTING GROUP, supra note 22, Chapter 3, app. 2.

43 See generally BOSTON CONSULTING GROUP, supra note 22, app. 2; PhRMA PROFILE 2001, supra note 10, ch. 3.


46 Id.

47 Although the reliability of the Institute of Medicine’s 1999 report has been called into question (available at www.IOM.edu), it is beyond dispute that medical mistakes are responsible for thousands of deaths per year. See Deaths Total From Medical Mistakes is a Matter of Dispute, Indianapolis News/Indianapolis Star, Mar. 31, 2002, at J1, available at 2002 WL 1569099; see also David Brown, The End of an Error? Big Business, Launching a New Era of Reform, & Preserving Hospitals to Cut Mistakes, WASH. POST, Mar. 26, 2002, at F01, available at 2002 WL 35785639. The problem is also pervasive outside of the United States. See
5) Many prevalent diseases remain untreatable with traditional pharmaceuticals. However, times are changing. Through fields such as genomics (identifying genes and gene function), proteomics (identifying protein function), and bioinformatics (the combination of biotechnology and information technology), the pharmaceutical industry anticipates churning vast amounts of data from voluminous numbers of samples and identifying as many as ten thousand drug targets over the next several years. This expectation is premised upon new sets of tools for discovering, mapping, and modifying genetic information—meaning tools for distinguishing gene expression and isolating which particular genes to study. Utilization of DNA chips, which are silicon chips embedded with multiple, distinguishable bits of DNA, has made large-scale screening possible. DNA chips can be used to test the samples of individuals for the presence of thousands of identified genetic variations and, alternatively, to screen hundreds of thousands of individuals with a shared phenotype characteristic to isolate and identify shared genetic expression. This technology has made it feasible to do comprehensive gene expression comparisons among large groups of people—e.g., a well-documented disease group such as the Framingham heart study patients, or even the population of Iceland. In fact, bioinformatics capabilities have inspired the formation of a consortium among pharmaceutical, biotech, and academic participants to compile data on the impact of variations of single nucleotide polymorphisms (SNPs), meaning single letters in the DNA blueprint—adenine ("A"), cytosine ("C"), guanine ("G"), or thymine ("T")—on susceptibilities to diseases and responsiveness to prescription drugs and/or drug combinations.

One consequence of this approach to pharmaceutical R&D is unprecedented precision. Reflective of this trend, those engaged in contemporary life science R&D have been filing a deluge of patent applications. More profound from a human health perspective, industry application is closely trailing the advancement of contemporary life science and, in turn, industry is financing and advancing this field of science—thereby moving us into an era of genetic precision in pharmaceutical development and prescription drug delivery.
Consequently, genetic testing is entering the medical setting as an accompaniment to drug delivery. For example, in 1998, Genentech, Inc. (South San Francisco, CA) introduced Herceptin into the marketplace for women with an aggressive form of breast cancer who also have over-expression of Her-2 neu; the market entry of Herceptin was accompanied by the commercial availability of a test to screen for over-expression of Her-2 neu. In January 2000, Visible Genetics Inc. (Toronto, CA) received national coverage approval from France for a genotyping kit for HIV that assists doctors in making the best use of available medicines. In 2002, the FDA approved the test for the U.S. market. In addition, Virologic (South San Francisco, CA) is manufacturing a homebrew version of this test, which enables patients and their physicians to determine whether they are infected with drug-resistant strains of HIV.

The research community, medical community, and even the general public should anticipate access to more pharmacogenomic testing capabilities in the foreseeable future. In fact, companies such as Orchid Pharmaceuticals (NJ), Pangea Systems, Inc. (Oakland, CA), and HySeq Inc (Sunnyvale, CA) have announced intentions to make information about genes available over the Internet for researchers first, and ultimately for consumers. Prior to his departure from Celera, Inc., the company that challenged the U.S. government-headed initiative in a race to map the human genome, founder Craig Venter stated that the ultimate Celera consumer would be the individual who will access the company’s databases to get information about him or herself and make more informed health care decisions. Some companies already have moved forward with business plans premised upon genetic profiling and direct-to-consumer interaction. For example, in the Summer of 2000, DNA Sciences launched a Web site to recruit people to donate their DNA to help identify genetic variations that cause disease, thereby compiling a database gene trust, a large statistical sample. In December 2000, DNA Sciences acquired PPGs, which had announced plans in the Fall of 2001 to offer a genetic test, the 2D6 test, directly to the public. The 2D6 test identifies the approximately ten percent of the population who are poor metabolizers of a broad array of prescription drugs.

III. IMPLICATIONS FOR THE DELIVERY OF HEALTH CARE AND THE ROLES OF PATIENTS, RESEARCH SUBJECTS, AND PROVIDERS

The shift from decades of dependence on pharmaceuticals crude by contemporary standards to generations of pharmaceuticals developed from potentially ten thousand plus drug targets will prove an impetus for ongoing changes in life science methodology. Genetic precision in drug development also will impact the practices and roles of commercial sponsors, research subjects, patients, and health care providers.

A. Basic Life Science R&D Implications

As stated above, in contemporary biomedical science, increasingly, less means more. Scientists have long appreciated that all di-
versity within the human species is attributable to a mere .1 percent of DNA. However, in March 2001, the science community determined that the human genome consists of approximately thirty thousand genes rather than the eighty to one hundred fifty thousand genes estimated throughout most of the 1990s. Presumably, individual genes do much more than anticipated before this count adjustment, meaning that gene function is a more intricate and complicated series of processes than previously appreciated.

The resulting reduction in scale and heightened intricacy in life science suggests that patenting at the level of expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs) is likely to increase even in the face of higher USPTO standards for utility and written disclosure. Other readily apparent implications of this heightened intricacy in life science R&D and utilization of this intensified commercial pressures on both industry and academia in an age of academic-industry collaborations and increasingly pervasive conflicts of interest that threaten the safety of research subjects and the integrity of data continued multiplication in the number of clinical trials initiated and more demand for trial subjects, and more direct communication between research sponsors and potential research participants to access both samples and subjects.

1. Access to Human Biological Samples

Many tracks of drug development research, including research utilizing pharmacogenomics, are dependent upon access to vast numbers of human subject samples and the resulting data. In fact, as discussed in Part II, ongoing scientific and commercial enthusiasm at the forefront of life science now centers on technical capabilities—microarrays, DNA chips, and other enabling technologies—that exponentially increase the number of human biological samples that can be run and the amount of data that can be generated and processed. The capability to run many thousands of genetic comparisons in the matter of minutes has jolted scientific and commercial demand to access and compile large-scale population databases.

The disconnect between the Clinton Administration and the Bush Administration has left unanswered many framed, highly controversial life science and health care policy and regulatory questions that may linger for years in spite of the intensity of the ongoing genetics revolution. One such question is whether the Common Rule will be expanded to encompass all human subject research, perhaps based upon the Commerce Clause, rather than just federally funded research. Another is whether "human subjects research" will be interpreted to include samples encrypted but ultimately identifiable.

88 See generally supra notes 94-61 and accompanying text (discussing trends in R&D that reflect these demands).

89 See id.

90 See id.


92 U.S. CONST, art. I, § 8, cl.3.

93 See National Bioethics Advisory Commission, Recommendations: Ethical and Policy Issues in Research Involving Human Participants (May 18, 2001) [hereinafter NBAC Recommendations] (proposing the establishment of one single, independent federal office to implement a unified, single set of regulations and guidance), available at http://bioethics.georgetown.edu/NBAC/pubs.html; see also Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (Apr. 18, 2001) (addressing whether U.S. regulations remain appropriate in the context of international research and the changing landscape of international research due to pressures on private companies to become more efficient in the conduct of research), available at http://bioethics.gov/clinical/.

94 See NBAC Recommendations, supra note 90. The primary regulatory issue is whether encrypted human biological samples will be treated as the equivalent of identifiable samples and therefore be fully subject to the requirements of informed consent and institutional review board (IRB) oversight. See 45 C.F.R, § 46.101 (2000) (referring to DHHS' protection
accountability to sample donors, the ability to generate exponentially more genetic information from a given sample will affirm and heighten medical privacy concerns.

2. Protection of Human Subjects

Meaningful pharmacogenomics research is expensive, as are human clinical trials. Even if pharmacogenomics can streamline trials, today, many more trials need financing. The pressure from shareholders to generate favorable data and to introduce breakthrough drugs to offset the loss of billion-dollar revenues due to patent expirations has heightened over the last few years, and the pressure continues to rise.

The United States’ framework to protect human subjects and complementary agency policies and enforcement practices generally:

60 Implementation of the HIPAA regulations will increase medical privacy protections but, at this time, whether these protections will offset the increased flow of genetic information remains an open question, especially since the Bush Administration has discarded the informed consent provision. See supra note 94.


62 See Malmovski, Institutional Conflicts, supra note 4, at n.94 (noting physicians may be paid reimbursement fees of thousands of dollars per patient). The “American Association of Health Plans generally encourages reimbursement for the routine costs of care associated with NIH-sponsored trials, and several large private health plans have been routinely covering cancer research trials conducted by the National Cancer Institute.” Id. at 55; see generally Francis H. Miller, Treating Doctors: Tricky Business When It Comes to Clinical Research, 81 IND. L. REV. 423, 425 (2001) (stating that “some drug and device manufacturers now compensate primary care physicians for enrolling their patients in clinical studies.”).

63 See Malmovski, Institutional Conflicts, supra note 4, at n.1 and accompanying text. To learn what is transpiring in the clinical trial segment of the drug development pipeline, see http://clinicaltrials.gov (detailing approximately 5,500 mostly government-funded clinical trials); http://cancer.gov/cancer_trials (exhibiting the National Cancer Institute’s clinical trial listing); http://acbs.org (the AIDS Clinical Trials Information Service (AC- TIS)); http://www.versitasmdicine.com (listing trials and standard treatments for numerous diseases); http://www.americasdoctor.com/directories/main.cfm (showcasing trials in seven disease categories, excluding cancer); and http://www.acuran.com/patient (developing lists of trials in various disease categories).

64 For discussion of the fundamental framework to protect human subjects (e.g., the Common Rule), the Institutional Review Board (IRB) system, and the Office of Human Research Protections (OHRP), see generally MALINOVSKI, BIOTECHNOLOGY, supra note 88; IRB REFERENCE BOOK, supra note 88.
ally predate the pervasive integration of academia and industry associated with contemporary life science. These regulatory regimes rely far too much upon self-compliance by institutions, which in turn defer to and depend upon self-compliance by the individuals engaged in the research that is supposed to be policed. Institutional policies, to the extent meaningful policies even exist, lack specificity regarding permissible relationships and practices and depend far too heavily upon disclosure to manage conflicts.

During the twilight of the Clinton Administration, sweeping bioethics reforms were proposed for human clinical trials. For example, in May 2000, the Clinton Administration released a plan to improve patient safety in clinical trials that calls for clear conflict-of-interest guidelines for doctors who stand to make money on their research. In May 2001, the National Bioethics Advisory Commission (“NBAC”) proposed establishing a single, independent office with jurisdiction over all (privately-funded, as well as federally-funded) domestic human subjects research with a single set of universal standards for IRBs.

President Bush did not appoint leadership for the Food and Drug Administration and National Institutes of Health until February.

See generally Malinowski, Institutional Conflicts, supra note 4, at 69 (noting the integration of academia and industry have increased productivity and patient care).

See id. at 64 (explaining the regulatory scheme in the United States and its low level of accountability due to reliance on self-compliance).

See generally id. at 66 (describing the majority of United States policies as ineffective). See generally id. at 66 (describing the majority of United States policies as ineffective).

See generally id. at 66 (describing the majority of United States policies as ineffective).


See generally Dr. Greg Koski, Director of the Office for Human Research Protections (OHRP) in HHS, called for the introduction of


101 See especially supra Part II.

102 See generally Malinowski, Snake Oil, supra note 3, at 31-33 & app. tbl. 1 (analyzing the uses of generic profiling). See also supra Part II.

103 Malinowski, Institutional Conflicts, supra note 4, at n.11; Malinowski, Snake Oil, supra note 3 at 33. See also Ann M. Thayer, Biotechnology for the Masses, CHEMICAL & ENGINEERING NEWS, Feb. 7, 2000, at 19 (discussing the use of software tools to capture data, which determines costs and improves use of the data collected in research).

104 See John Pople, Harvard Researchers Head a China Gene Study, WASH. POST, Aug. 9, 2001, at A14 (noting the allegations about a Harvard professor’s human-subject research, including allegations of taking blood from Chinese farmers without informed consent and not providing promised medical care).

105 See Genentech’s Eys Pharmacogenomics Business in Japan, CHEMICAL BUS. NEWS BRIEF, Nov. 24, 2000, at 12 (stating that a joint venture between two U.S. companies, Varigenics and Covance, was formed “to provide services to Japanese pharmaceutical producers interested in overseas clinical development activities”).

106 See Decode Genetics, Inc. available at www.decode.com (describing Decode also as having established Decode Cancer to commercialize diagnostics and therapeutics).
3. Conflicts of Interest

The inclusion of a conflicts of interest provision in the U.S. regulatory regime—a compliment and extension of regulations for technology transfer, to protect human subjects, and to ensure research integrity—places tremendous reliance on self-policing by researchers. To maintain compliance with the regulations, institutions must establish conflict of interest policies that require disclosure of any financial interests. These policies are subject to ongoing review and evaluation by institutional review boards (IRBs) to ensure compliance with federal and institutional policies.

To support academic-industry synergies moving forward, relevant regulatory regimes must be strengthened. This observation has been made in recent years by controversies involving the disclosure of adverse events in clinical trials and even other human studies. The adoption of policies and procedures in the drug development process is crucial to ensuring the integrity of the research process.

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116 Federal thresholds have been established by the Department of Health and Human Services (DHHS), National Institutes of Health (NIH), to define "significant financial interest" as "any agreement or arrangement that will give rise to financial gain or loss in excess of $5,000 to any individual, including but not limited to salary or other payments for services, including services of a nonmonetary nature, such as services as a consultant, advisor, research associate, or other similar service; equity interests; security options, warrants, or other rights to acquire stock, securities, or other interests in a company; and intellectual property rights." This is to prevent overlapping and to ensure that there is no conflict of interest.

117 See Malinowski, Institutional Conflicts, supra note 4, at 58 (discussing that university audits are rare in a system of heavy reliance on individual researcher oversight).

118 See Korn, Conflicts of Interest in Biomedical Research, 284 JAMA 2224 (Nov. 1, 2000).


120 See Malinowski, Institutional Conflicts, supra note 4, at 54 (stating that websites such as those of the National Institute of Health and the National Library of Medicines provide access to clinical trials, which link patients with trials).

121 This transparency is attributable in part to the United States' official, FDA-managed clinical trial website, at http://www.clinicaltrials.gov. For additional clinical trial websites, see supra note 99.
pipeline, both patients and providers will more readily look to clinical trials for health care options. Decisions by the government and other payers to cover clinical trial-related medical costs in a reliable manner are encouraging this trend. Muddying the threshold between clinical trials and standard of care will have a profound impact on professional responsibility, liability, and health care finance.

C. Genetic Profiling as an Accompaniment to Prescription Pharmaceuticals

The day when the neighborhood pharmacist routinely tailors commercially available pharmaceuticals to account for each person's SNP idiosyncrasies may be decades removed. Nevertheless, introduction of genetic tests to make prescription drug choices thus far is simply a glimpse into a foreseeable future. Choices thus far is simply a glimpse into a foreseeable future. Pharmacogenomics as a R&D methodology will bring forth meaningful capabilities will be utilized by the medical community to engage in individually tailored health care delivery and prevention with significant health outcome improvements. Subscriber services to inform individuals about the latest SNP identifications that could impact their research ongoing manner are already under development. Such databases are presently available to members of the research and services are presently available to members of the research community, and the mission of the ongoing work of the well-funded and diligent SNP consortium is to churn out a voluminous number of genotype-phenotype (genetic-physical characteristic) connections.

The use of pharmacogenomics and pharmacogenetics by the health care community will intensify and add new dimensions to many standing law and policy issues. These issues include genetic exceptionalism in both law and regulation, education of the health care provider community, market acceptance, and patient access.

1. Genetic Exceptionalism

Predictive genetic tests manufactured and sold to others to perform are regulated by the FDA as medical devices. However, predictive genetic tests performed by their manufacturers and made available to others as a service, which are known as "homebrew tests," escape FDA regulation and are arguably not meaningfully regulated otherwise. This regulatory exceptionalism was made all-too-clear in 1996 and 1997 when several biotech companies engaged in commercializing predictive genetic tests for breast cancer premised upon links between the disease and BRCA1 and BRCA2 variations, without data to establish the clinical utility of these tests.

See also Malinowski, Snake Oil, supra note 3, at 32 (explaining that bioinformatics has used software to create data libraries).


See also Malinowski, Snake Oil, supra note 3, at 44 (explaining the only meaningful federal oversight of homebrew testing is under the CLIA, or the Clinical Laboratory Improvement Amendments, the scope of which is limited to regulating the proficiency/accuracy of testing and administrative requirements). See generally Amy Hwang, Genetic Testing: Institutional Reluctance and Public Guardianship, 53 FORDHAM L. J. 555, 556-57 (1996) (citing the FDA has repeatedly taken the position that it will not regulate "kits," even though it regulates testing services conducted at centers and laboratories). See Genetic Testing Under the Clinical Laboratory Improvement Amendments, 65 Fed. Reg. 25,928 (May 4, 2000) (announcing that the CLIA Committee recommended the creation of a genetic testing specialty); CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAAC), GENERAL RECOMMENDATIONS FOR QUALITY ASSURANCE PROGRAM FOR LABORATORY MOLECULAR GENETIC TESTS (Aug. 31, 1999); SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING (SACGT), ENHANCING THE OVERSIGHT OFGENETIC TESTS RECOMMENDATIONS OF THE SAGCT (July 2003), available at http://www4.od.nih.gov/cda/sacgt.htm.
conception for women in general.\textsuperscript{136} Consequentially, patient groups, bioethicists, and policy makers expressed concern that industry would engage in premature commercialization of predictive genetic tests for a multitude of multigenic disorders in a similar manner.\textsuperscript{137} The outcome was an adverse market response to those initial tests and their manufacturers, professional and public criticism, and genetic exceptionalism in state and federal law.\textsuperscript{138} Given that most genetic tests have multiple potential uses,\textsuperscript{139} definitional ambiguity is prevalent in this legislation.\textsuperscript{140} Therefore, genetic exceptionalism may provide a significant market barrier to the commercial availability of genetic profiling technologies in general and, consequently, for utilization of pharmacogenomics to improve the delivery of health care.\textsuperscript{141}

2. Health Care Provider Competency

The transition from fee-for-service into managed care has imposed time and other commercial pressures on the United States health care community.\textsuperscript{142} Even before the spread of managed care throughout the 1990s, concerns were raised about the failure of most medical school curricula to educate health care providers to deliver care in the midst of the genetics revolution.\textsuperscript{143} The explosive advancement of biotechnology from the research bench into the market has validated many of these concerns.\textsuperscript{144} "In light of the towering and still rising wave of information, the all-knowing general practitioner is not a contemporary possibility."\textsuperscript{145}

The advent of pharmacogenomics now may overwhelm the medical community with an even more pervasive set of challenges. Although managed care generally has embraced diagnostic testing and preventive screening, an intense deluge of additional testing associated with a generation of much more expensive pharmaceuticals would prove difficult to absorb.\textsuperscript{146} Moreover, the market introduction of a multitude of innovative pharmaceuticals accompanied by genetic profiling and added decision making, a jolt in pharmaceutical complexity attributable to genetic precision, changes in longstanding disease classifications, and the commingling of clinical care and ongoing clinical research will necessitate significant changes in the delivery of care. Rather than making doctors and nurses assume this entire burden, it is likely that pharmacists and non-physician clinicians will be stepping into an expanded role in the health care process.

\textsuperscript{136} See Malinowski, Snake Oil, supra note 3, at 36 (stating that the absence of clinical utility can lead to test takers unknowingly subjecting themselves to possible overtreatment, false reassurances, and discrimination by insurers and employers).

\textsuperscript{137} See id. at 35-37 (describing the marketing of tests to detect mutations in the BRCA1 gene "to predict susceptibility to the occurrences of some hereditary forms of breast cancer.").

\textsuperscript{138} See id. at 34-37 (explaining how in the midst of a series of federal legislative and administrative initiatives, states enacted an entanglement of genetics legislation). For a concise and informative overview of the kinds of legislation states have enacted, see Williams F. Mulholt, "Organizational Attributes of Stated Law Reform". Journal of Legal Education. 39 (1989).

\textsuperscript{139} See id. at 35-37 (explaining how in the midst of a series of federal legislative and administrative initiatives, states enacted an entanglement of genetics legislation). For a concise and informative overview of the kinds of legislation states have enacted, see Williams F. Mulholt, "Organizational Attributes of Stated Law Reform". Journal of Legal Education. 39 (1989).

\textsuperscript{140} See generally Michael J. Malinowski, Boundaries, Medical Ethics and the Ad- vance of a New Era in Medical Ethics: The Ethics of Diagnosis, 32 J. L. & Med. 321, 326 (1996), reprinted in TAKING SIDES: CLASHING VIEWS ON CONTROVERSIAL ETHICAL ISSUES (Carol Levine ed., 7th ed. 1997) (stating that "as a result of third-party payment of health care costs, patient consum- ers have become indifferent and insensitive to the prices of services and the costs of treatment, seldom considering price and cost even when they undergo elective diagnostic tests and surgeries.").


\textsuperscript{142} Michael J. Malinowski, Foreword: Academic-Industry Collaborations in the Clinic, 8 WASH. L. REV. 1-2 (2003) (commenting how the market is driven by "academic-industry alliances.").

\textsuperscript{143} Malinowski, Institutional Conflicts, supra note 4 at 54.

\textsuperscript{144} For an excellent treatment of the health care complexities of clinical application of ad- vances in human genetics, see generally GENETICS IN THE CLINIC: CLINICAL, ETHICAL, AND SOCIAL IMPLICATIONS FOR PRIMARY CARE (Mary Mahowald et al. eds., 2003) (hereinafter GENETICS IN THE CLINIC).
3. Market Acceptance and Patient Access

Conceivably, the public may embrace and directly pay for selective genetic profiling services—such as screening to anticipate reactions to major pharmaceuticals and to manage drug interactions—to the extent necessary to make providing those services commercially viable. Market acceptance also may be realized in part through viable. Market acceptance also may be realized in part through medical community participation in life science R&D utilizing medical community participation in life science R&D utilizing pharmacogenomics. Major medical centers with access to samples pharmacogenomics. Major medical centers with access to samples and patients are positioned to aggressively pursue these opportunities and, when such institutions embrace technology transfer and are likely and, when such institutions embrace technology transfer and are likely commercial collaborations, their portfolios of agreements are likely to encompass a considerable amount of clinical research.

Nevertheless, many in the medical community are more familiar with the confidentiality, privacy, and potential discrimination issues associated with predictive genetic testing than the technology itself. Educating the medical community about the multitude of intricacies associated with the broad generation of drugs developed through pharmacogenomics could prove a daunting challenge for pharmaceuticals, and could add an additional dimension of complexity to drug prescribing. The dangers of over-reliance on genetic profiling include over and under dosing and false assurances. These oversights can lead to failures to closely monitor drug interactions or to make necessary dosage adjustments and drug substitutions over time. In addition, the significant streamlining of clinical trials may heighten provider dependence on compiled Phase IV data while the pharmaceuticals are being taken by patients. Even more fundamental, introducing drugs genetically tailored to fit only into the eye of a traditional disease classification may prove problematic for a medical provider community accustomed to traditional disease classification, as studies suggest, that the use of predictive genetic testing with clinical utility for many common disorders is decades removed from the present realities of managed care.

147 See supra note 68-76 and accompanying text (identifying some emerging Internet services, including genetic screening services to improve drug reactions and identify potential problems from drug interactions).

148 See Liz Kowalczyk, Larvatec Licensing Deals with Drug, Biotech Firms are Raising Ethics Issues for Hospitals, BOSTON SUN DAY GLOBE, Mar. 24, 2002, at C1 (stating “[h]ospitals have become increasingly interested, particularly since managed care restricted their income during the 1990s and heated competition for patients fostered a more entrepreneurial attitude.

149 See supra note 68-76 and accompanying text (identifying some emerging Internet services, including genetic screening services to improve drug reactions and identify potential problems from drug interactions).

150 See generally GENETICS IN THE CLINIC, supra note 146; Lee M. Silver, The Meaning of Genes and “Genetic Rights” 40 JURISPRUDENCE J. 9, 11-12 (1999) (explaining what genes are and how they compare to others’ genes).

151 See infra Part IV; see supra Part III. See generally Kahn, supra note 22, at 20 (identifying a number of market variables that bear upon the market performance of the biotechnology and pharmaceuticals sectors).

152 For example, today’s technologies for cancer include Herceptin, a drug that has proven helpful for many patients with previously untreatable cases of breast cancer at a cost of approximately $20,000 per patient, and a $10,000 wafer chip that delivers chemotherapy directly into a patient’s brain. See Pam Abramowitsch, The Financial Impact of Genomics, TREE BOND BUYER, Dec. 13, 2000, p. 18, 2000 WB. 30707201. See also Juma et al., supra note 33.

153 See generally Pincusow, supra note 50 and accompanying text.

154 See Malinowski, Institutional Conflicts, supra note 4, at 18 (stating that the "use of pharmacogenomics, bioinformatics, and related technologies will result in pharmaceuticals tailored to individual genetic profiles, streamlined therapeutic use, regulatory approval and labeling limitations...

155 See Madeleine, FDA Regulation, supra note 28, at 224.
erated by market use, the dynamic nature of the human genome in response to environmental stimuli, and the need to make pharmaceutical dosage and drug changes over time, the cost of monitoring could prove significant.

This climate and the raging controversy over drug pricing suggest that genetic profiling as an accompaniment to drug delivery will have to enter the marketplace with sound evidence of clinical utility in order to be accepted.154 Widespread medical community acceptance is likely to depend heavily upon the safety, efficacy, and clinical utility of the pharmaceuticals developed with pharmacogenomics that carry genetic profiling into the marketplace.155

IV. PROPOSALS FOR LEGISLATIVE AND REGULATORY REFORM

Admittedly, today’s life science enabling technologies and commercial investment in applying those technologies make gauging tomorrow’s health care a speculative endeavor even for experts.156 Nevertheless, recent history is telling: biotechnology and genetic medicine have influenced the delivery of care in jolting ways over the last decade.157 Therefore, in the context of this period of development, additional proposals may be prudent.158 This article has identified many of the issues associated with this technology. Thus article has identified many of the issues associated with this technology. This article has identified many of the issues associated with this technology. This article has identified many of the issues associated with this technology.

154 See Malinowski, Snake Oil, supra note 3, at 47 (charting how to an unstable drug market). Cf. Malinowski, Snake Oil, supra note 3, at 47 (charting how to an unstable drug market). Current enabling techniques allow industry players to develop new research possibilities.

155 In 1995, there were only eight biotech-derived pharmaceuticals on the market. Today, there are over 100. For identification of the present drug development pipeline, see http://www.pharma.org (site of the Pharmaceutical Research and Manufacturers of America (PhRMA), the world’s leading pharmaceutical trade organization); http://www.bios.org (site of the Biotechnology Industry Organization (BIO), the world’s leading biotechnology industry trade organization). For identification of the biotech drugs on the market in 1995, industry trade organization).

156 See generally Richard D. Lamm, Universal Health Care Coverage: A Tax-Front War, 22 J. Legal Med. 225, 225-27 (June 2001) (stating that 16% of the United States population has no health insurance, and that this uninsured population tends to be more sick on average than those people with health insurance).

157 See Arthur Jones, Stretching to the Limit, Nat’l CATHOL. REP., Feb. 22, 2002, at 3, 2002 WL 10150411 (explaining that there are approximately forty million uninsured/insufficiently insured citizens in the United States that many of those joining the ranks of the uninsured are working Americans).
One might argue, therefore, that there is a moral imperative in addition to a professional obligation to bridge law and policy with meaningful fieldwork (meaning laborious fact gathering) in both life science R&D and health care delivery, and to thereby proactively address foreseeable health law, policy, and bioethics challenges in a pragmatic manner. Given the life and death ramifications of health law and policy, in addition to academic theory and intellectual capabilities, those in the field must and approach issues with a "critical mass" of practical knowledge in: (a) regulation and legislation along the entire R&D continuum from the laboratory bench to the health care marketplace, (b) the economic and other realities of life science R&D, (c) health care delivery, and (d) the health care marketplace.

In recent scholarship, this author and others have proposed regulatory law and institutional reforms to address many of the challenges that will be exacerbated by the advent of pharmacogenomics, including access to human biological materials, protection of human subjects, conflicts of interest, and commingling of clinical care and clinical research.168 The reforms proposed by this author include revisiting the present state legislative scheme encompassing predictive genetic testing,169 introducing reliable federal information management systems for both human subject protection and technology transfer,170 coupling federal oversight capabilities with enforcement (such as compliance audits in both human subject protection and technology transfer),171 and bridging grant compliance and technology transfer application within health science institutions.172


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166 See generally Michael J. Malinowski, Symposium, Conflicts of Interest in Clinical Research: Legal and Ethical Issues, 8 WENDELL L. SVAAR, J. 47 (2001); Malinowski, Snake Oil, supra note 3, at 41-46 (explaining his thesis in "A Proposal For Regulatory Reform").
167 See generally Malinowski, Snake Oil, supra note 3, at 41.
168 See generally Malinowski, Institutional Conflicts, supra note 4, at 69-73 (suggesting new changes in "Proposals for Reform").
169 See generally Malinowski, Snake Oil, supra note 3, at 36 (describing how enabling technologies have had an explosive impact on biotechnology R&D—perhaps mostly to the surprise of the health care community).
170 See supra note 22 and accompanying text.
171 See supra note 3 and accompanying text.
172 Patent law provides a meaningful example, for intellectual property policy innately presumes insight about and sensibly towards markets, economic reality, and the actual practices and circumstances of technology innovation. Cf. PHILIP W. CHU, PATENTS OF CHEMICALS: PHARMACEUTICALS AND BIOLOGICALS: FUNDAMENTALS OF GLOBAL LAW, PRACTICE AND STRATEGY (1999) (stating that "in the previous edition of this book [the publishers] have benefited greatly from the input provided by many experienced practitioners in the field, as well as from the feedback of readers of the previous edition").
173 Arguably, the U.S. patent regime did not anticipate the shifting spectrum of scientific research and practice advances in the field of the science introduced by fields such as biotechnology, genomics, and bioinformatics over the last several years and, in hindsight, patentable categories may have been bioinformatics.
174 See Utility Examination Revised Standards for written description and utility in genetics. See Utility Examination Revised Standards for written description and utility in genetics
This article has framed a series of additional questions which culminate in the following: Given opportunities to introduce more meaningful preventive care and to improve health care outcomes through commercialization of pharmacogenomics, to what extent should the legal and health care environments be made more welcoming to this technology to accelerate its widespread use? Even if this technology introduces significant short-term costs, should these costs be absorbed by a health care system already failing to cover millions of citizens? If yes, then at what price? Consider that by shattering traditional disease classifications,\(^{172}\) raising the costs of pharmaceuticals,\(^{174}\) and introducing a genetic profiling element to drug prescribing and, more generally, to the delivery of care,\(^{175}\) pharmacogenomics is likely to push United States health care into an era of much more pervasive and extreme tiering of coverage and access. Also, given that under such circumstances many genetic profiling services may be sought and purchased directly by the public,\(^{176}\) it is time to consider introducing workable yet meaningful safeguards for direct communication between the public and commercial providers of genetic profiling services.\(^{177}\)

The medical, life science, and legal communities must work through the entanglement of variables encompassed by these questions to come up with algorithms that work on a collective level, especially since the United States continues to lack reliable federal regulatory oversight of predictive genetic testing services.\(^{178}\) Criteria must be developed to guide health care providers, the public, and payers to make decisions about clinical utility and responsible medical use of genetic profiling technologies. For example, although meaningful genetic profiling capabilities presumably will be developed and introduced in a sporadic manner over the next few decades, genetic profiling ultimately should prove as pervasive as

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\(^{172}\) See Malinowski, Institutional Conflicts, supra note 4, at n.21; see also Malinowski, FDA Regulations, supra note 20, at 224.\(^{174}\) See Malinowski, Institutional Conflicts, supra note 4, at n.21 (explaining that cost hikes can impede industry innovation).\(^{175}\) See generally Malinowski, Snake Oil, supra note 3, at 31 (commenting that individualized medical treatment is a notion "decades removed").\(^{176}\) See supra note 132 and accompanying text.\(^{178}\) See generally Malinowski, Snake Oil, supra note 3, at 33-41 (considering "The Consequences of Genetic Exceptionalism").