2 Hous. J. Health L. & Pol'y 31-63

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Houston Journal of Health Law & Policy
ISSN 1534-7907

Law, Policy, and Market Implications of Genetic Profiling in Drug Development

Michael J. Malinowski*

Introduction

Completion of a map of the human genome[1] 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]

* Ernest and Iris Eldred Associate Professor of Law Science, and Public Health, Paul M. Hebert Law Center, Louisiana State University. This article originated in presentations made at the University of Arizona College of Pharmacy in February 2001 and at the Louisiana State University in February 2002. The author would like to thank those who participated in these forums and shared their comments. The author also would like to thank his students at Hofstra University School of Law during the spring 2002 semester for interactions that enriched this article. This article was submitted for publication in April 2002, and does not necessarily reflect events thereafter.

[1] On June 26, 2000, U.S. government-led and privately funded teams of scientists jointly announced their completion of a rough map of the human genome. *See What's News World-Wide*, Wall St. J. Eur., June 27, 2000, *available at* 2000 WL-WSJE 21064884. *See generally* 291 Sci. 1145 (February 16, 2001) (issue entitled "The Human Genome"); 409 Nature 745 (Feb. 15, 2001) (issue dedicated to the release of a draft map of the human genome). *See also International Human Genome Sequencing Consortium, Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860, 872 fig. 9 (Feb. 15, 2001) (draft map of the human genome); Michael D. Lemonick, *The Genome is Mapped. Now What?*, Time, July 3, 2000, at 24-29. Information about the Human Genome Project may be obtained from the Internet site of the National Human Genome Research Institute (NHGRI), *available at* www.nhgri.nih.gov (last visited Mar. 24, 2002).

[2] For a discussion of DNA chip technology and how it is accelerating drug development that is readily accessible to non-scientists, see Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology 73-78, 225 tbl. B.1 (Perseus Publishing, 2000).

[3] For discussion of the range of enabling technologies being utilized for identification of genetic expression, see Michael J. Malinowski, *Separating Predictive Genetic Testing From Snake Oil: Regulation, Liabilities, and Lost Opportunities*, 41 Jurimetrics 23, 31-33, 47 tbl. 1 (2000) [hereinafter Malinowski, *Snake Oil*]. *See generally* Aris Persidis, *Biotechnology in a Snapshot*, 18 Nature Biotechnology IT2 (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 Riordan, *Patents: An Obsession with DNA and the Human Genome Leads to Development of a Technology*, N.Y. Times,

The pharmaceutical and biotechnology industries are utilizing genetics-based research to improve decision-making and to streamline the drug development process, which has given rise to a field known as pharmacogenomics.[4] In simplest terms, pharmacogenomics is the "study of the impact of genetic characteristics on the health care of populations who share the characteristic(s) at issue."[5] Because of this approach to drug development, society should anticipate the incremental market introduction of generations of drugs with unprecedented genetic specificity and reduced side effects.[6] These drugs will be accompanied by heavy utilization of genetic profiling in the delivery of health care.[7] 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.[8] "The study of the impact of genetic characteristics on the health care of individuals who possess the characteristic(s) at issue" is a field known as pharmacogenetics.[9]

Mar. 18, 2002, at C2 (profiling the work of Eugene Chan, founder and chairman of U.S. Genomics).

[4] Pharmacogenomics encompasses identifying cell function at the genetic level and using predictable cellular response to chemical stimuli at the genetic level to drive drug development. *See* Malinowski, *Snake Oil*, *supra* note 3, at 49 tbl.2. This field is likely to accelerate drug discovery and introduce some clinical trial cost savings, but it is also likely to divide traditional disease classifications and shorten the market lifespan of drugs through the more timely introduction of follow-on technology and market substitutes. *See* Michael J. Malinowski, *Institutional Conflicts and Responsibilities in an Age of Academic-Industry Alliances*, 8 WIDENER L. SYMP. J. 47 n.21 (2001) [hereinafter Malinowski, *Institutional Conflicts*]; Ronald Rosenberg, *Development of Drugs Seen Faster, Cheaper*, BOSTON GLOBE, June 5, 2001, at D1-D2, *available at* 2001 WL 3936608; *see also infra* Part III.C.2 (arguing that pharmacogenetics is producing many challenges that the medical community will have to face, such as forcing pharmacists and medical personnel to assume increased responsibilities). *But see* Arti K. Rai, *The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost, and Access in the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 173 (2001) (suggesting that cost savings from genomics will generate a market windfall that should be used to "scale back" patent protection for pharmaceuticals).

[5] *See* Malinowski, *Snake Oil*, *supra* note 3, at 49 tbl. 2.

[6] *See generally id.* at 47 tbl. 1.

[7] *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* Leroy Hood & Lee Rowen, *Genes, Genomes, and Society*, *in* GENETIC SECRETS 21 (Mark A. Rothstein ed., 1997).

[8] Malinowski, *Snake Oil*, *supra* note 3, at 31-33.

[9] *Id.* 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 derived from 483 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, consequentially, 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 obtainable from individual samples;[16]

7) Fracturing of traditional disease classifications and recognition of health conditions not yet fully identified;[17]

8) Increased specificity in FDA drug labeling and restrictions on approved uses;[18]

[10] *See* PHARMACEUTICAL INDUSTRY PROFILE 2001: A CENTURY OF PROGRESS 14 (2001) [hereinafter PhRMA PROFILE 2001], *available at* www.phrma.org; PhRMA, PHARMACEUTICAL INDUSTRY PROFILE 2000 (2000) [hereinafter PhRMA PROFILE 2000]; Ronald Rosenberg, *Data Bottleneck Slowing Drug Discovery*, BOSTON GLOBE, June 20, 2001, at D4; *see infra* Part II ("Trends in Pharmaceutical R&D"); *see generally* ERNST & YOUNG, CONVERGENCE: THE BIOTECHNOLOGY INDUSTRY REPORT (2000).

[11] *See infra* Part III.A.1 ("Access to Human Biological Samples").

[12] *See infra* Part III.B ("Metamorphosis of Clinical Research").

[13] *See infra* notes 99, 125 and text accompanying notes 124-27.

[14] *See infra* Part IV ("Proposals for Legislative and Regulatory Reform"); *see generally* Malinowski, *Institutional Conflicts*, *supra* note 4 at 64-73 (introducing proposals for regulatory reform).

[15] *See infra* Part III.A, III.A.1 ("Access to Human Biological Samples"), Part III.A.2 ("Protection of Human Subjects"), and Part III.A.3 ("Conflicts of Interest").

[16] *See infra* Part III.A.1 ("Access to Human Biological Samples").

[17] *See infra* Part III.C.2 ("Health Care Provider Competency").

[18] *See infra* note 49 and accompanying text.

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;[19]

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 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

[19] *See infra* Part III.C.3 ("Market Acceptance and Patient Access").

[20] *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at n.21; Michael J. Malinowski, *FDA Regulation of Biotechnology Products for Human Use*, *in* 1 ENCYCLOPEDIA OF ETHICAL, LEGAL, AND POLICY ISSUES IN BIOTECHNOLOGY 215, 224 (Thomas J. Murray & Maxwell J. Mehlman eds., 2000) [hereinafter Malinowski, *FDA Regulation*].

[21] This sentiment in favor of price controls on pharmaceuticals was strong enough to prompt the National Institute of Health (NIH) to issue a report opposed to introducing additional conditions on biomedical research funding. *See generally* DEP'T HEALTH & HUMAN SERVS., NAT'L INST. OF HEALTH, NIH RESPONSE TO THE CONFERENCE REPORT REQUEST FOR A PLAN TO ENSURE TAXPAYERS' INTERESTS ARE PROTECTED (July 2001), *available at* http://www.nih.gov/news/070101wyden.htm; *see also* Milt Freudenheim & Melody Petersen, *The Drug-Price Express Has Run Into a Wall*, N.Y. TIMES, Dec. 23, 2001, at 1 (reporting market resistance to expensive new drugs in the absence of significant clinical utility benefits to offset price increases).

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-

[22] *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 Munger 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).

[23] 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 anti-depressant 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 dose version of Prozac. For identification of other pharmaceutical products losing patent protection from 2000 through 2003, including expiration date and sales information, see ROBBINS-ROTH, *supra* note 2, at 164-165 tbl. 20.1.

[24] For example, in December 2001, 29 attorneys general filed suit against Bristol-Myers Squibb to release 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).

[25] *See* Generic Pharmaceutical Association (GPhA), *at* www.gphaonline.org (noting that while brand name prescription drugs represented 55% of all prescriptions, they consumed more than 90% of drug therapy dollars spent at retail).

[26] Drug Price Competition and Patent Restoration Act of 1984 ("Hatch-Waxman Act"), Pub. L. No. 98-417, 98 Stat. 1585 (codified in scattered sections of 15 U.S.C., 21 U.S.C., 28 U.S.C., and 35 U.S.C.). *See generally* John Hudson, *Generic Take-Up in the Pharmaceutical Market Following Patent Expiration: A Multi-Country Study*, 20 INT'L REV. L. & ECON. 205, 211 (2000).

[27] "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 ("Phase IV data")—and without assuming the enormous risks, costs, and time-consuming market development challenges undertaken by drug innovators.[29]

Moreover, in spite of law reforms in favor of globalization of 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

[28] According to the Pharmaceutical Research and Manufacturers of America ("PhRMA"), the amount of pharmaceutical sales allocated to R&D will have reached 18.5 percent in 2001 (compared with 17.4 percent in 1999), meaning that in 2001 the industry spent $26.3 billion on R&D. *See* PHRMA PROFILE 2001, *supra* note 10, at ch. 2. According to PhRMA, the time from synthesis of a new drug to market approval has stretched to 14.2 years in the 1990s. *Id*. (relying upon data from the Tufts Center for Drug Development). For details regarding the FDA's requirements to establish safety and efficacy for a range of products, *see* www.fda.gov.

[29] *See supra* note 28. *See also* MICHAEL J. MALINOWSKI, BIOTECHNOLOGY LAW, BUSINESS, & REGULATION ch. 11 (Aspen Law & Business 1999 & Supps. 2001, 2002) (describing the content of the phases).

[30] Agreement on Trade Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Legal Instruments—Results of the Uruguay Round, vol. 31, 33 I.L.M. 81, 84 (1994) (expressing a desire to reduce obstacles to international trade through protection of intellectual property rights).

[31] *See generally* Calestous Juma et al., *Global Governance of Technology: Meeting the Needs of Developing Countries*, 22 INT. J. TECH. MGMT. 629, 646 (2001); Jeffrey D. Sachs, *Balms for the Poor*, THE ECONOMIST, Aug. 14, 1999, at 63.

an aggressive form of breast cancer,[32] Cerezyme for Gaucher's disease,[33] Pulmozyme for cystic fibrosis,[34] and protease inhibitors for AIDS patients[35] are juxtaposed with the proliferation of deaths in developing economies from highly preventable and treatable conditions such as basic nutritional deficiencies[36] and malaria.[37] Public health and delivery of care inadequacies in countries such as the Russian Republic, other former members of the Soviet Union, and China are causing once treatable conditions such as tuberculosis to take new, virulent and generally ominous forms.[38] Even in the shadow of impending GATT/TRIPS implementation, the wildfire spread of AIDS and associated deaths in African nations has renewed demands for compulsory licensing of pharmaceutical-owned

[32] Information about Herceptin is *available at* www.herceptin.com. Herceptin generally is administered in combination with Taxol, and the total cost of this cocktail is approximately $12,000 per patient for a six-month course ($6,000 per drug). *See* Beezy Marsh, *The Miracle Cocktail: New Drugs Cocktail Can Help Women to Live Longer*, DAILY MAIL, May 16, 2001, *available at* 2001 WL 21128992.

[33] The world's most expensive medicine, Cerezyme, costs approximately $175,000 per patient annually. *See* Dan Gerstenfeld, *Teva to Market Treatment for Gaucher's Disease*, THE JERUSALEM POST, Nov. 21, 2001, *available at* 2001 WL 6617162.

[34] Information about Pulmozyme may be obtained from its manufacturer, Genentech, Inc. of South San Francisco, *at* www.gene.com. *See* J.D. Kleinke, *The Price of Progress: Prescription Drugs in the Health Care Market*, HEALTH AFF. 4360, Sept. 1, 2001, *available at* 2001 WL 10696964 (including Pulmozyme in a category of expensive new drugs that lower short-term health care costs but guarantee higher costs in the long run—"the economics of smoking in reverse").

[35] A year's therapy in the United States costs approximately $8,000. *See Latest Developments in HIV Diagnosis and Treatment*, PULSE 60, Feb. 11, 2002, *available at* 2002 WL 13571781.

[36] Genetic modification, though opposed by many in developed economies, could prove a cost effective means to overcome some of these public health challenges. For example, golden rice is a genetically modified strain of rice designed to overcome debilitating vitamin A deficiency. *See* David Lague, *Biotechnology*, FAR. E. ECON. REV. 34, Apr. 4, 2002, *available at* 2002 WL-FEER 5169787.

[37] "Of a total $70 billion spent on health care research worldwide in 1998, for instance, only $100 million was set aside for malaria research (about a tenth of the cost of the U.S. Department of Defense's recent 'experiment' of intercepting a ballistic missile with a ground-launched exo-atmospheric kill vehicle)." *Rights of Access*, 19 NATURE BIOTECHNOLOGY 693 (Aug. 2001). Although highly treatable and preventable with contemporary therapeutics, malaria remains pervasive in developing economies and, with AIDS and tuberculosis, has become an international public health priority and the subject of a multibillion-dollar global fundraising initiative—"The Global Fund to Fight AIDS, Tuberculosis, and Malaria," which is a private foundation. *See* Christopher Newton, *HH Secy. Thompson to Visit Africa*, ASSOCIATED PRESS, Mar. 29, 2002, *available at* 2002 WL 17189950; *Bill Gates, Bono Call on Leaders at World Economic Forum*, M2 PRESSWIRE, Feb. 1, 2002, *available at* 2002 WL 4158486.

[38] "Tuberculosis is turning out to be one of the major killers of the new millennium and is probably the most serious threat to public health after AIDS." *TB Continues to be Scourge of the Century*, THE TIMES OF INDIA, Mar. 27, 2002, *available at* 2002 WL 17725854.

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.[39] The leading AIDS drug manufacturers within the pharmaceutical industry have made major concessions but have been unable to completely fend off generic competitors.[40] Consequentially, these nations have reaffirmed the pharmaceutical industry's apprehensions about interacting with the governments of developing economies and widened the life science gap yet further, thereby ensuring future disputes over access to innovative pharmaceuticals and tensions over recognition of intellectual property rights.[41] The absence of meaningful life science capabilities in many biologically diverse areas of the world raises global susceptibility to public health challenges.[42]

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.[43] The overall revenue allocated to R&D has risen from 11% to 18.5% over the last twenty years,[44] and overall pharmaceutical investment in R&D has risen from approximately $2 billion in 1991 to $30.5 billion in 2001.[45]

Nevertheless, the pharmaceutical sector's aggressive embrace of the precision in drug development introduced through biotechnology and fields such as pharmacogenomics will have market consequences for these multinational pharmaceutical behemoths whose existence is premised upon voluminous market scale and products

[39] 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 manufacturers for safe AIDS drugs, which included a large Indian producer of generics and three smaller European ones.").

[40] *See* McNeil, *supra* note 39, at A3.

[41] *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 or accessed full information about those deliberations, it would be presumptuous to declare that more satisfactory, workable alternatives to this outcome were overlooked. Therefore, it must be acknowledged that alleviating ongoing human suffering and death attributable to AIDS in developing economies and undertaking measures to contain the accompanying threat to global public health at the present time by forcing industry concessions may justify escalating the longer-term challenge of closing the life science technology gap between developed and developing economies.

[42] *See generally* LAURIE GARRETT, THE COMING PLAGUE (1994); JUDITH MILLER, STEPHEN ENGELBERG, WILLIAM BROAD, GERMS: BIOLOGICAL WEAPONS AND AMERICA'S SECRET WAR (2001).

[43] *See supra* note 28; *see also* Malinowski, *Institutional Conflicts*, *supra* note 4, at 48-49.

[44] *See* PhRMA PROFILE 2001, *supra* note 10, at ch. 2.

[45] *See id.*

that generate billion-dollar revenue streams on an annual basis.[46] As addressed below, decades of extraordinary profitability from broad market exploitation, including extensive off-label use by physicians, of pharmaceuticals developed from several hundred drug targets to treat all human diseases is the past, not the future, of commercial life science.[47]

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.[48] There is wide variation in patient responsiveness for most pharmaceuticals, ranging from non-responsiveness to severe adverse events from the standard of care dosage. Consequentially:

1) Physicians have practiced broad off-label discretion, moving use of most pharmaceuticals well beyond the clinical trial design for safety and efficacy and resulting FDA labeling;[49]

2) Our aging population now is testing the limit of our knowledge about drug combinations and interactions;[50]

3) Dosage and drug combinations raise patient-by-patient challenges for physicians;[51]

4) Estimates for the health care costs associated with unintended reactions to pharmaceuticals have reached as much as $100 billion annually;[52] and

[46] *See* Malinowski, *FDA Regulation*, *supra* note 20 at 224; Malinowski, *Institutional Conflicts*, *supra* note 4, at n.21. *See generally* BOSTON CONSULTING GROUP, *supra* note 22, Chapter 3, app.2.

[47] *See infra* notes 151-154 and accompanying text.

[48] *See generally* BOSTON CONSULTING GROUP, *supra* note 22, app.2; PhRMA PROFILE 2001, *supra* note 10, ch. 3.

[49] *Companies Balance Risks, Rewards of Off-Labeling*, FOOD & DRUG LETTER, Mar. 15, 2002, 2002 WL 12321164 .

[50] Mary Desmond Pinkowish, *Prescribing for Older Patients: 5 Points to Remember*, PATIENT CARE 45, *available at* 2000 WL 100711936 (Aug. 15, 2000).

[51] *Id.*

[52] 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 Death Total from Medical Mistakes is a Matter of Dispute*, INDIANAPOLIS NEWS/INDIANAPOLIS STAR, Mar. 31, 2002, at J01, *available at* 2002 WL 16980099; *see also* David Brown, *The End of an Error? Big Business, Launching a New Era of Reform, is Pressuring Hospitals to Cut Mistakes*, WASH. POST, Mar. 26, 2002, at F01, *available at* 2002 WL 17585639. The problem is also pervasive outside of the United States. *See*

5) Many prevalent diseases remain untreatable with traditional pharmaceuticals.[53]

However, times are changing. Through fields such as genomics (identifying genes and gene function),[54] proteomics (identifying protein function),[55] and bioinformatics (the combination of biotechnology and information technology),[56] 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.[57] 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.[58] Utilization of DNA chips, which are silicon chips embedded with multiple, distinguishable bits of DNA, has made large-scale screening possible.[59] DNA chips can be used to test the samples of individuals for

Sarah Lyall, *More Deaths In England Due to Error, Report Says*, N.Y. TIMES, Dec. 20, 2001, at A6 (reporting that approximately 1,200 people died in public hospitals in Britain last year due to mistakes in prescribing and administering medications).

[53] *Harnessing Genes, Recasting Flesh*, THE PHARMACEUTICAL CENTURY, *available at* http://pubs.acs.org/journals/pharmcent/Ch8.html. In spite of the resources invested over the past several decades to combat diseases responsible for the highest levels of mortality in the United States, namely heart disease and cancer, those diseases remain formidable challenges. As of March 2001, heart disease was responsible for 35% of all deaths among those 65 and older, and cancer was responsible for 22% of the deaths in this age group. CTRS. FOR DISEASE CONTROL AND PREVENTION, NAT. CNTR FOR HEALTH STATISTICS, TRENDS IN CAUSES OF DEATH AMONG THE ELDERLY *available at* www.cdc.gov/nchs/data/agingtrends/0/death.pdf.

[54] Malinowski, *Snake Oil*, *supra* note 3, at tbl. 1.

[55] *Id*. at tbl. 2. IBM's Blue Gene can crack the genetic code for proteins from start to end. Eric Stawiski, *The Biologist Meets the Computer Scientist*, WORLD & I, Mar. 1, 2002, p. 137143, *available at* 2002 WL 9015548. For an illustration of how IBM is using its supercomputing technology for biomedical research, *see IBM/Physiome Sign Supercomputing/Biological Modeling Pact*, MAINFRAME COMPUTING (Oct. 1, 2001), *available at* 2001 WL 12586424.

[56] Malinowski, *Snake Oil*, *supra* note 3, at tbl. 1.

[57] *See supra* note 10 and accompanying text. As stated earlier, the approximately 3,000 traditional pharmaceuticals on the market have been developed from just 483 drug targets. PhRMA, INDUSTRY PROFILE 2001, *supra* note 10, at v.

[58] *See generally* Malinowski, *Snake Oil*, *supra* note 3 at 31-33; PhRMA, INDUSTRY PROFILE 2001, *supra* note 10 at ch.9; *see* BOSTON CONSULTING GROUP, *supra* note 22, at 53-55, app.1.

[59] The basic methodology is to use the process of hybridization (predictable nucleotide bonding between A&T, C&G) and probes—short nucleotide chains that have a signaling enzyme that glows when the probe hybridizes (i.e., the gene of interest is present)—to isolate and identify instances of genetic expression. ROBBINS-ROTH, *supra* note 2, at 73-74. Today, scientists are able to access commercial DNA chips with the capacity to screen for more than 6,000 specific genetic sequences (DNA arrays). Malinowski, *Snake Oil*, *supra* note 3, at 32. Affymetrix has introduced a commercial chip with the capacity to screen for 400,000+ arrays by 2003 (a 1999 prediction that may already have been realized). *See* ROBBINS-ROTH, *supra* note 2, at 73-81; *see also* David Stipp, *Gene Chip Breakthrough Microprocessors Have Reshaped our Economy, Spawned Vast Fortunes and Changed the Way We Live. Gene Chips Could be Even Bigger*, FORTUNE, March 31, 1997, at 56.

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.[60] 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 thytosine ("T")—on susceptibilities to diseases and responsiveness to prescription drugs and/or drug combinations.[61]

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.[62] 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 deliv-

[60] *See infra* notes 115 and 148.

[61] *See* Orchid Biosciences, Inc., *at* http://www.orchid.com. Consider that, if each nucleotide base letter in your DNA blueprint was the size of a letter in standard typewritten text, your DNA blueprint would be a sentence spanning from Portland, Oregon to Chicago, Illinois. A SNP is just *one* of those billions of letters. Tom Abate, *The Gene Age/Inside Ourselves/Two Groups on Verge of Reading the Entire Human Gene Code*, S. F. CHRON., Apr. 25, 2000, at A1.

[62] *See* Michael J. Malinowski, *The Commodity of Intellectual Property in the Risky Business of Life Science*, 41 JURIMETRICS 414 & nn. 33-34 (1999) (book review essay). The PTO now issues 70% more patents—approximately 170,000 in 1999—than it did a decade ago. *See* UNITED STATES PATENT & TRADEMARK OFFICE, *Annual Reports: 1999 Annual Report*, *available at* http://www.uspto.gov/web/offices/com/annual/index.html; *see also* Peter Coy, *The 21st Century Corporation*, BUS. WEEK, Aug. 28, 2000, at 78. Patent applications for biotechnology, organic chemistry, and pharmaceuticals have nearly doubled from 1996 to 2000 (reaching 32,705 in 2000), and approximately two-thirds of the 2000 applications were for genomics patents. *See* UNITED STATES PATENT & TRADEMARK OFFICE, *Annual Reports: 2000 Annual Report*, *available at* http://www.uspto.gov/web/offices/com/annual/index.html. The PTO has added 800 examiners and estimates a 25% increase in filings for 2001.

ery.[63] Consequentially, genetic testing is entering the medical setting as an accompaniment to drug delivery.[64] 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.[65] 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.[66] In 2002, the FDA approved the test for the U.S. market.[67] 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.[68]

The research community, medical community, and even the general public should anticipate access to more pharmacogenomic testing capabilities in the foreseeable future.[69] 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.[70] Prior to his departure from Celera, Inc.,[71] the company that challenged the U.S.

[63] *See generally* Malinowski, *Snake Oil*, *supra* note 3, at 26; PhRMA PROFILE 2001, *supra* note 10 at ch.2; PhRMA PROFILE 2000, *supra* note 10 at ch. 2.

[64] *See generally* Malinowski, *Snake Oil*, *supra* note 3.

[65] *See generally* ROBERT BAZELL, HER-2: THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER 175-186 (1998); *see also FDA Approves DAKO Herceptest to Identify Potential Patients for Herceptin, the New Breast Cancer Treatment Drug from Genentech*, BUS. WIRE 20:26:00 (Sept. 25, 1998).

[66] *See* Andrew Pollack, *When Gene Sequencing Becomes a Fact of Life*, N.Y. TIMES, Jan. 17, 2001, at C1; *see also* Malinowski, *Snake Oil*, *supra* note 3, at 31 n.31.

[67] *See* Visible Genetics Inc., *FDA Grants Market Clearance of HIV Genotyping System*, BIOINDEX, (Apr. 10, 2002), *available at* 2002 WL 18689534; *see also* Tom Abate, *The Economics of Genetic Testing/The Race to Develop New Ways to Detect Disease is As Much About Cost as it is About Technology*, S.F. CHRON., Feb. 10, 2002, at G1, *at* 2002 WL 4012496 (detailing information on the strengths and weaknesses of Celera).

[68] *See id.*

[69] *See generally* Malinowski, *Snake Oil*, *supra* note 3, at 32-33.

[70] *See id.*

[71] David Shook, *Celera: A Biotech That Needs a Boost: The Onetime Genomics Highflier has to Replace Departed Founder Craig Venter and Ramp Up Its Drug Development Unit*, BUS. WEEK, Mar. 1, 2002, *available at* 2002 WL5145033.

government-headed initiative in a race to map the human genome,[72] 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.[73] 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.[74] In December 2000, DNA Sciences acquired PPGx, which had announced plans in the Fall of 2001 to offer a genetic test, the 2D6 test, directly to the public.[75] The 2D6 test identifies the approximately ten percent of the population who are poor metabolizers of a broad array of prescription drugs.[76]

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[77] 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-

[72] *See supra* note 1.

[73] Lawrence M. Fisher, *Surfing the Human Genome: Data Bases of Genetic Code Are Moving to the Web*, N.Y. TIMES, Sept. 20, 1999, at C1. Subsequently, Venter has moved on to found two institutes. *See* Nicholas Wade, *Thrown Aside, Genome Pioneer Plots a Rebound*, N.Y. TIMES, Apr. 30, 2002, at D1, D6.

[74] DNA Sciences, *at* http://www.dna.com.

[75] *DNA Sciences Inc.*, MED AD NEWS, Aug. 1, 2001, at 16, *available at* 2001 WL 26968874.

[76] David Stipp, *A DNA Tragedy*, FORTUNE, Oct. 30, 2000, at 170, *available at* 2000 WL 24218519; Cinda Becker, *Special Report: The DNA Rx*, MODERN HEALTHCARE, Aug. 28, 2000, at 24, *available at* 2000 WL 8169272.

[77] *See supra* note 10 and accompanying text.

versity within the human species is attributable to a mere .1 percent of DNA.[78] 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.[79] 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.[80] Other readily apparent implications of this heightened intricacy in life science R&D and utilization of bioinformatics include raised demand for human biological samples and access to pedigree information and family histories,[81] 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,[82] continued multiplication in the number of clinical trials initiated and more demand for trial subjects,[83] and more direct communication between research sponsors and potential research participants to access both samples and subjects.[84]

1. *Access to Human Biological Samples*

Many tracks of drug development research, including research utilizing pharmacogenomics, are dependent upon access to vast

[78] *See* www.amnh.org/exhibitions/genomics; *see also* Francis S. Collins et al., *New Goals for the U.S. Human Genome Project: 1998-2003*, 282 SCIENCE 682, 683 (1998).

[79] Gene Weingarten, *Genetic Leftovers: Those Extra DNA Strings May Hold Keys to Oddities*, HOUS. CHRON., Mar. 23, 2001, at 1, *available at* 2001 WL 3007837.

[80] In January 2001, the agency announced new "Utility Examination Guidelines" and "Written Description Guidelines" intended to make it more difficult to patent genes. *See* Utility Examination Guidelines, 66 Fed. Reg. 1092-1099, 1097-99 (Jan. 5, 2001) (setting forth specific standards); Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, P1, "Written Description" Requirement, 66 Fed. Reg. 1099 (2001). These guidelines clarify that a claimed invention must have a specific and substantial utility that is credible or a readily apparent, well-established utility. *See* 66 Fed. Reg. at 1092-1099 (2001).

[81] *See infra* section III.A.1.

[82] *See infra* sections III.A.2., III.A.3.

[83] *See infra* section III.B.

[84] *See infra* notes 99, 125 and accompanying text (identifying web sites that make clinical trial information directly accessible by the general public).

numbers of human subject samples and the resulting data.[85] 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.[86] 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.[87]

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[88] will be expanded to encompass all human subject research, perhaps based upon the Commerce Clause,[89] rather than just federally funded research.[90] Another is whether "human subjects research" will be interpreted to include samples encrypted but ultimately identifiable.[91]

[85] *See generally supra* notes 54-61 and accompanying text (discussing trends in R&D that reflect these demands).

[86] *See id.*

[87] *See id.*

[88] The Department of Health and Human Services' policy to protect human subjects, known as the Common Rule, is codified at 45 C.F.R § 46 (2000). For a technical discussion about human subject protection regulations and their implementation, *see* MICHAEL J. MALINOWSKI, BIOTECHNOLOGY: LAW, BUSINESS, & REGULATION § 9.02 (Aspen Law & Business 1999 & Supps. 2001, 2002); *see generally* PRICEWATERHOUSE COOPERS, LLP, INSTITUTIONAL REFERENCE BOARD (IRB) REFERENCE BOOK (Michele K. Russell-Einhorn & Thomas Puglisi, eds., 2001).

[89] U.S. CONST. art. 1, § 8, cl.3.

[90] *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/.

[91] *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 subjected to the requirements of informed consent and institutional review board (IRB) oversight. *See* 45 C.F.R. § 46.101 (2000) (referring to DHHS' protection

During the Clinton Administration, the anticipated expansion and meaningful enforcement of human subject protection regulations and debate over the implementation of the Health Insurance Portability and Accountability Act ("HIPAA")[92] raised the commercial viability of companies in the business of providing an "ethically sound" alternative to the vast human biological material repositories compiled over the last several decades.[93] However, in March 2002, the Bush Administration discarded the HIPAA informed consent requirement as "unworkable," thereby alleviating some immediate angst in the health care delivery and life science communities.[94] Nevertheless, given the timeline for developing a pharmaceutical,[95] there now is regulatory pressure on those engaged in life science R&D to either use wholly unidentifiable samples or to introduce significant complexity and expense—e.g., purchase the services of commercial suppliers of human biological materials—which presumably will be folded into escalating drug costs. In the absence of implementation and enforcement of reliable regulatory safeguards around sample collection and use that ensure

for human subject regulations); 21 C.F.R. 50.20 (2001) (referring to FDA informed consent regulations). *See also* DEP'T OF HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTECTIONS, COMPLIANCE OVERSIGHT PROCEDURES (2000), *at* http://www.ohrp.osophs.dhhs.gov/compovr.htm.

[92] *HHS Proposes Changes that Protect Privacy, Access to Care; Revisions Ensure Privacy Protections, Removing Obstacles to Care*, U.S. NEWSWIRE, Mar. 21, 2002, 2002 WL 4575666 [hereinafter *HHS Proposes Changes*].

[93] Examples of these commercial suppliers include The First Genetic Trust, *available at* www.firstgenetic.net, and Genomics Collaborative, Inc., *available at* www.dnarepository.com. *See* Jeffrey Krasner, *Gene Pooling: Company Builds World's Largest Library of Genetic Material*, BOSTON GLOBE, Aug. 22, 2001, at F1. Many of the hundreds of millions of samples held in preexisting repositories were collected during the course of routine diagnostic and medical procedures under a theory of medical waste and donor abandonment and without meaningful consent. Eric Niiler, *Surgical Refuse is Research Treasure*, THE S.D. UNION-TRIBUNE, Dec. 6, 2000, at F1. In addition to commercial suppliers, some teaching hospitals are compiling central tissue banks with contemporary informed consent practices to become future suppliers. *See* Jeffrey Krasner, *Partners HealthCare Planning Tissue Bank: Hospital Group Cites Research Potential*, BOSTON GLOBE, Sept. 4, 2001, at D1.

[94] *See HHS Proposes Changes*, *supra* note 92. Subsequently, the Bush administration changed the burden for collecting written informed consent to notice of privacy policies. *See* Jennifer Kulynych & David Korn, *Use and Disclosure of Health Information in Genetic Research: Weighing the Impact of the New Federal Medical Privacy Rule*, 28 AM. J.L. & MED. 309, 322-23 (discussing the ramifications of the proposed rule changes); *see also* 45 C.F.R. § 164.508 (2002) (reflecting that these policy changes become effective on Oct. 15, 2002).

[95] *See supra* note 28 (PhRMA estimates that, during the 1990s, the time required to develop a new drug stretched to more than 14 years).

accountability to sample donors,[96] the ability to generate exponentially more genetic information from a given sample will affirm and heighten medical privacy concerns.[97]

2. *Protection of Human Subjects*

Meaningful pharmacogenomics research is expensive, as are human clinical trials.[98] Even if pharmacogenomics can streamline trials, today, many more trials need financing.[99] 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.[100]

The United States' framework to protect human subjects and complementary agency policies and enforcement practices[101] gener-

[96] 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.

[97] *See generally* Chris Meyers et al., *Genomics: Implications for Health Systems/ The Effect of Genomics on Health Services Management: Ethical and Legal Perspectives*, 17 FRONTIERS OF HEALTH SERV.S MGMT. 316 (2001).

[98] *See* Malinowski, *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, *Trusting Doctors: Tricky Business When It Comes to Clinical Research*, 81 B.U. L. REV. 423, 425 (2001) (stating that "some drug and device manufacturers now compensate primary care physicians for enrolling their patients in clinical studies").

[99] *See* Malinowski, *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/clinical_trials (exhibiting the National Cancer Institute's clinical trial listing); http://actis.org (the AIDS Clinical Trials Information Service (ACTIS)); http://www.veritasmedicine.com (listing trials and standard treatments for numerous diseases); http://www.americasdoctor.com/clintrials/main.cfm (showcasing trials in seven disease categories, excluding cancer); and http://www.acurian.com/patient (developing lists of trials in various disease categories).

[100] *See* Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: A Contractarian Model of Access*, 11 YALE J. ON REG. 401, 442-43 (1994) (describing the need for private experimental drug companies to develop sales revenues and make a reasonable profit). *See supra* notes 22-25 and accompanying text.

[101] 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* MALINOWSKI, BIOTECHNOLOGY, *supra* note 88; IRB REFERENCE BOOK, *supra* note 88.

ally predate the pervasive integration of academia and industry associated with contemporary life science.[102] 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.[103] Institutional policies, to the extent meaningful policies even exist,[104] lack specificity regarding permissible relationships and practices and depend far too heavily upon disclosure to manage conflicts.[105]

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.[106] 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 rules.[107] Similarly, Dr. Greg Koski, Director of the Office for Human Research Protections (OHPR) in HHS, called for the introduction of universal standards for IRBs.[108]

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

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

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

[104] *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).

[105] *See generally* Mildred K. Cho et al., *Policies on Faculty Conflicts of Interest at US Universities*, 284 JAMA 2203, 2208 (2000) (reporting on an empirical survey indicating that the vast majority of research institutions have failed to establish relevant policies because the policies lack specificity).

[106] *See* PRESS RELEASE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, SECRETARY SHALALA BOLSTERS PROTECTIONS FOR HUMAN RESEARCH SUBJECTS (May 23, 2000), *available at* http://www.hhs.gov/news/press/2000pres/20000523.html (noting policies will be developed to require disclosure of financial interest in a clinical trial to potential participants); Donna Shalala, *Protecting Human Subjects—What Must Be Done*, 343 NEW ENG. J. MED. 808, 809 (2000).

[107] See *NBAC Recommendations*, supra note 90 (proposing the establishment of one independent federal office to implement a unified, single set of regulations and guidance), *available at* http://bioethics.gov/press/finalrecomm5-18.html.

[108] *See* OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP) DIVISION OF ASSURANCES AND QUALITY IMPROVEMENT, QUALITY IMPROVEMENT PROGRAM (April 15, 2002), *at* http://ohrp.osophs.dhhs.gov/humansubjects/qip/qipdesc.pdf.; *see generally* http://ohrp.osophs.dhhs.gov/references/koskibio.pdf (detailing the biography of Dr. Greg Koski).

ary and May of 2002, respectively, and subsequently these agencies presumably have merely shifted from limbo into a period of transition.[109] Although President Bush has established a new Council in Bioethics, thus far, this commission has fixated on the issue of human cloning.[110] Nevertheless, research continues to rage onward, with increased utilization of genetic profiling.[111] Never have as many clinical trials been underway, and pharmacogenomics is being embraced in clinical research to streamline both costs and time.[112] In fact, clinical research sponsored by U.S. companies to advance pharmacogenomics has become a burgeoning, global endeavor. Examples include Millennium Pharmaceuticals' undertakings in China, which has triggered considerable anxiety over human subject participation,[113] and the joint venture in Japan by Variagenics and Covance in November 2000.[114] Similarly, Iceland's DeCode Genetics, which has collaborations with several U.S. interests, has established Encode, a subsidiary specializing in pharmacogenomics studies.[115]

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[109] Lester M. Crawford, Jr. was appointed to serve as FDA Deputy Commissioner on Feb. 25, 2002. *See* DEPT. OF HEALTH AND HUMAN SERVICES, *Lester M. Crawford Jr. Named FDA Deputy Commissioner* (Feb. 25, 2002) *available at* http://www.hhs.gov/news/press/2002pres/20020225.html. Elias Adam Zerhouni was appointed to serve as the Director of the NIH on May 20, 2002. *See* NIH, *Zerhouni Assumes Leadership of the National Institutes of Health* (May 20, 2002), *available at* http://www.nih.gov/news/pr/may2002/od-20.

[110] The President's Council on Bioethics, *available at* http://bioethics.gov/ (describing their meeting agendas for February and January 2002, which covered the issue of cloning).

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

[112] Malinowski, *Institutional Conflicts*, *supra* note 4, at n.1; Malinowski, *Snake Oil*, *supra* note 3 at 33. *See also* Ann M. Thayer, *BioInformatics for the Masses*, CHEMICAL & ENGINEERING NEWS, Feb. 7, 2000, at 19 (discussing the use of software tools to capture data, which decreases costs and improves use of the data collected in research).

[113] *See* John Pomfret, *Harvard Rebukes Head of 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).

[114] *See Covance Eyes Pharmacogenomics Business in Japan*, CHEMICAL BUS. NEWS BASE, Nov. 24, 2000, at 12 (stating that a joint venture between two U.S. companies, Variagenics and Covance, was formed "to provide services to Japanese pharmaceutical producers interested in overseas clinical development activities").

[115] *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 principal investigators and their institutions.[116] Trust is a questionable assurance mechanism to police researchers and institutions exposed to commercial incentives such as royalty and equity interests.[117] Contemporary commercial influences, including heavy dependence upon industry for financing, application expertise, and access to a multitude of proprietary enabling technologies, also have exacerbated a preexisting entanglement of non-financial pressures:

> These pressures, not primarily financial, include the desire for faculty advancement, to compete successfully and repetitively for sponsored research funding, to receive accolades from professional peers and win prestigious research prizes, and to alleviate pain and suffering. . . All of these nonfinancial pressures may generate conflicts by creating strong bias toward positive results, and all of them may more powerfully influence faculty behavior than any prospect of financial enrichment.[118]

To support academic-industry synergies moving forward, relevant regulatory regimes must be strengthened. This observation has been made all too evident in recent years by controversies including the death of human subjects given less than forthright information about adverse events in primate and even other human studies,[119] instances of doctors enrolling and treating patients in

[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." *See* 42 C.F.R. § 50.603(1), (3)-(5) (2000) (defining a "significant financial interest" as "anything of monetary value, including, but not limited to, salary or other payments for services. . .equity interests. . .and intellectual property rights," but not including aggregated payments of $10,000 and/or ownership interest in excess of 5% in a single entity); 21 C.F.R. §§ 54.1-54.6 (2001) (outlining financial disclosures by clinical investigators through the FDA). *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at 72-73 and accompanying text (addressing both NIH and FDA guidelines). However, the agencies rely heavily upon institutions to actually manage conflicts. *Id*. at 69.

[117] *See generally* 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] David Korn, *Conflicts of Interest in Biomedical Research*, 284 JAMA 2234 (Nov. 1, 2000).

[119] *See* Gelsinger v. Trustees of the Univ. of Pa., Case No. 0009018885 (Ct. Com. Pl., Phila. County, filed Sept. 18, 2000), *at* http://www.sskrplaw.com/links/healthcare2.html ["Gelsinger Complaint"]. Following the death of Jesse Gelsinger, the American Society of Gene Therapy (ASGT) prohibited researchers from taking equity interests or stock options in companies which sponsor the researchers' gene therapy trials. Furthermore, the Association of American Medical Colleges (AAMC) announced the formation of a task force to address conflicts of interest issues, and the American Medical Association (AMA) adopted

clinical studies paid for by the companies they own,[120] disputes between academics and their industry sponsors over data,[121] and pressures on universities to loosen conflict-of-interest rules.[122] In the absence of significant regulatory reform, escalating commercial pressures will increase risks to human subjects and research integrity.[123]

B. Metamorphosis of Clinical Research

Genetic precision in bench research is rapidly spilling over into clinical trials, where experimentation and treatment (meaning clinical research and clinical care) are integrating.[124] Clinical research has entered an era of transparency, meaning that information about clinical trials is online and accessible to the general public, and the public is seeking access.[125] As breakthrough treatments for presently untreatable conditions mature in the drug development

a policy on conflicts of interest calling on all medical centers to develop guidelines to avoid perceived and actual conflicts. *See* AMER. SOC'Y OF GENE THERAPY (ASGT), POLICY OF THE AMERICAN SOCIETY OF GENE THERAPY ON FINANCIAL CONFLICT OF INTEREST IN CLINICAL RESEARCH (2000), *at* http://www.asgt.org/policy/index.html; AM. MED. ASS'N, COUNCIL ON ETHICAL & JUDICIAL AFFAIRS, CONFLICTS OF INTEREST: BIOMEDICAL RESEARCH, OP. E-8.031 (1999), at http://www.ama-assn.org/apps/pf_online/. . .TM&hxt_pol=policy files/CEJA/E-8.01.HTM&; Malinowski, *Institutional Conflicts*, *supra* note 4, at 69-70.

[120] *See* Gelsinger Complaint, *supra* note 119; *see also* Sheryl Gay Stolberg, *Biomedicine Is Receiving New Scrutiny as Scientists Become Entrepreneurs*, N.Y. TIMES, Feb. 20, 2000, at A26 (noting that according to the FDA, this practice was becoming increasingly pervasive in the field of gene therapy prior to the death of Jesse Gelsinger).

[121] For example, the company Immune Response and medical researchers at the University of California at San Francisco and Harvard University have been engaged in a high-profile dispute over publication of negative data from the Phase III trial of Remune, an anti-HIV drug. *See* Eric Niiler, *Company, Academics Argue over Data*, 18 NATURE BIOTECHNOLOGY 1235 (Dec. 2000).

[122] *See* Katherine S. Mangan, *Harvard Medical School Will Keep Its Conflict-of-Interest Policies*, CHRON. HIGHER EDUC., June 9, 2000, at A36 (noting that Harvard University even considered lessening its relatively strict standards, but then decided against that proposal). In fact, Harvard has joined several other renowned medical schools in drafting joint conflicts of interest guidelines. *See* Katherine S. Mangan, *Medical Schools Draft Guidelines for Preventing Conflicts of Interest*, CHRON. HIGHER EDUC., Feb. 23, 2001, at A36.

[123] *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at 72 (suggesting that the Bush Administration continue reforms to improve accountability in biomedical research). *See generally infra* Part IV.

[124] *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 online access to clinical trials, which link patients with trials).

[125] This transparency is attributable in part to the United States' official, FDA-managed clinical trial web site, *at* http://www.clinicaltrials.gov. For additional clinical trial web sites, see *supra* note 99.

pipeline, both patients and providers will more readily look to clinical trials for health care options.[126] 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.[127]

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, market introduction of genetic tests to make prescription drug choices thus far is simply a glimpse into a foreseeable future.[128] Pharmacogenomics[129] as a R&D methodology will bring forth meaningful pharmacogenetics[130] capabilities. In turn, these capabilities will be utilized by the medical community to engage in individually tailored health care delivery and prevention with significant health outcome improvements.[131] Subscriber services to inform individuals about the latest SNP identifications that could impact their responses to commercially available drugs and drug interactions in an ongoing manner are already under development.[132] Such databases and services are presently available to members of the research

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[126] *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at 53-54 (describing the public perception of clinical trials as creating breakthrough treatments).

[127] HEALTH CARE FINANCING ADMIN., MEDICARE COVERAGE POLICY-CLINICAL TRIALS, FINAL NATIONAL COVERAGE DECISION, *at* http://www.hcfa.gov/coverage/8d2.htm; DEP'T OF HEALTH & HUMAN SERVS., HEALTH CARE FINANCING ADMIN., HCFA FACT SHEET, MEDICARE COVERAGE ROUTINE COSTS OF BENEFICIARIES IN CLINICAL TRIALS (2000), *at* http://www.hcfa.gov/medlearn/ctfs13.pdf (stating that Medicare beneficiaries would not lose their coverage by enrolling in clinical trials in an effort to promote more innovations through clinical trials). *See also* Malinowski, *Institutional Conflicts*, *supra* note 4, at 55-56 (noting that government policy is supportive of clinical care). *See generally* SUSAN QUINN, HUMAN TRIALS: SCIENTISTS, INVESTORS, AND PATIENTS IN THE QUEST FOR A CURE (Perseus 2001) (detailing a case study of the company AutoImmune which emphasized the impact of clinical trials on patients awaiting innovative treatments).

[128] Genetic profiling as an accompaniment to drug delivery is made tangible by present applications of such technology. *See supra* notes 64-68 and accompanying text.

[129] *See supra* notes 4-5 and accompanying text.

[130] *See supra* note 9 and accompanying text.

[131] *See supra* note 8 and accompanying text.

[132] *See supra* notes 69-76 and accompanying text.

community, and the mission of the ongoing work of the well-financed and diligent SNP consortium is to churn out a voluminous number of genotype-phenotype (genetic-physical characteristic) connections.[133]

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.[134] 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.[135] 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 this con-

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[133] *See* THE SNP CONSORTIUM LTD., SINGLE NUCLEOTIDE POLYMORPHISMS FOR BIOMEDICAL RESEARCH *at* http://snp.cshl.org (stating that the Consortium's mission is to research and publicize SNPs, not that the general public will have access to this scientific information). *See also* Malinowski, *Snake Oil*, *supra* note 3, at 32 (explaining that bioinformatics has used software to create data libraries).

[134] Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (codified as amended at 15 U.S.C. § 55 (1994) and in sections of 21 U.S.C.). *See* Malinowski, *Snake Oil*, *supra* note 3, at 43-44 (recommending that Congress revise the Medical Devises Act to enable and encourage the FDA to regulate gentic tests more broadly).

[135] *See* 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* Anny Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 556-57 (1998) (stating 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 (CLIAC), 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 OF GENETIC TESTS: RECOMMENDATIONS OF THE SACGT (July 2000), available at http://www4.od.nihgov/oba/sacgt.htm.

nection for women in general.[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 multigenetic disorders in a similar manner.[137] The outcome was an adverse market response to these initial tests and their manufacturers, professional and public criticism, and genetic exceptionalism in state and federal law.[138] Given that most genetic tests have multiple potential uses,[139] definitional ambiguity is prevalent in this legislation.[140] Therefore, genetic exceptionalism may prove a significant market barrier to the commercial availability of genetic profiling technologies in general and, consequently, for utilization of pharmacogenetics to improve the delivery of health care.[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

[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 over-treatment, false assurances, and discrimination by insurers and employers.

[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.").

[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, organized overview of the kinds of legislation states have enacted, *see* William F. Mulholland, II & Ami S. Jaeger, *Genetic Privacy and Discrimination: A Survey of State Legislation*, 39 JURIMETRICS J. 317, 317-26 (1999) (noting that the most prohibited actions under this legislation include some combination of the following: genetic testing in general; requiring or requesting a genetic test or information; disclosing the results of a genetic test to third parties without prior informed consent; discharging, refusing to hire, or refusing to promote by employers on the basis of the results of genetic tests; affecting terms, conditions, or disbursement of benefits based upon the results of genetic tests; refusing to consider an application; refusing to issue or renew an existing policy; classifying information derived from a genetic test as a preexisting condition; charging higher rates or premiums; and discriminating charges in brokerage fees or commissions). Exceptions are commonly made for genetic testing in a court proceeding and genetic research. *Id.* at 318-19.

[139] Malinowski, *Snake Oil*, *supra* note 3, at n.24 and accompanying text. Consider that a genetic test for over expression of Her2-neu could be used: (1) in a woman with breast cancer to determine whether she should consider taking certain medications for treatment, such as Herceptin; (2) in a healthy woman with a family history of breast cancer to help assess susceptibility to the disease and perhaps to determine whether she should take medication as a preventive measure; or (3) perhaps by a potential mother with a family history of breast cancer to screen embryos before undergoing in vitro fertilization.

[140] *Id.* at 28-29 (highlighting that scientific definitions of "predictive genetic testing" work relatively well in a regulatory context).

[141] *See generally id.* at 30.

health care community.[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.[143] The explosive advancement of biotechnology from the research bench into the market has validated many of these concerns.[144] "In light of the towering and still rising wave of information, the all-knowing general practicioner is not a contemporary possibility."[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.[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 long-standing 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.

[142] *See generally* Michael J. Malinowski, *Capitation, Advances in Medical Technology, and the Advent of a New Era in Medical Ethics*, 22 AM. J.L. & MED. 331, 336 (1996), *reprinted in* TAKING SIDES: CLASHING VIEWS ON CONTROVERSIAL BIOETHICAL ISSUES (Carol Levine ed., 7th ed. 1997) (stating that "as a result of third-party payment of health care costs, patient consumers have become indifferent and insensitive to the prices of services and the costs of treatments, seldom considering price and cost even when they undergo elective diagnostic tests and surgeries.").

[143] Michael J. Malinowski & Robin J.R. Blatt, *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 TUL. L. REV. 1211, 1245-1246 (1997) (explaining that the current generation of health care providers do not possess the skills to interpret predictive genetic tests).

[144] *See* Michael J. Malinowski, *Foreword: Academic-Industry Collaborations in the Clinic*, 8 WIDENER L. SYMP. J. ii, ii-iii & nn. 1-7 (2001) (commenting how the market is driven by "academic-industry alliances.").

[145] Malinowski, *Institutional Conflicts*, *supra* note 4, at 54.

[146] For an excellent treatment of the health care complexities of clinical application of advances in human genetics, *see generally* GENETICS IN THE CLINIC: CLINICAL, ETHICAL, AND SOCIAL IMPLICATIONS FOR PRIMARY CARE (Mary Mahowald et al. eds., 2001) [hereinafter GENETICS IN THE CLINIC].

3. *Market Acceptance and Patient Access*

Conceivably, the public may embrace and directly pay for select 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.[147] Market acceptance also may be realized in part through medical community participation in life science R&D utilizing 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 commercial collaborations, their portfolios of agreements are likely to encompass a considerble amount of clinical research.[148]

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.[149] Educating the medical community about the multitude of intricacies associated with a broad generation of drugs developed through pharmacogenomics could prove a daunting challenge for the life science industry. Clinical use of most predictive genetic testing requires considerable interpretation, and pharmacogenomics

[147] *See supra* notes 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, *Lucrative Licensing Deals with Drug, Biotech Firms are Raising Ethics Issues for Hospitals*, BOSTON SUNDAY 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."); *see also* Liz Kowalcsyk, *Medical Schools Join Forces: Harvard, Others Aim to Give Drug Firms Faster OK's on Clinical Trials*, BOSTON GLOBE, July 28, 2000, at C1 (reporting on an alliance between Harvard and four other medical schools to counter the private industry's efforts to dominate human research on new medical treatments). Medical academia is attempting to reclaim its influence in clinical research, which has been diminished over the last decade through the emergence and explosive growth of the global contract research organization ("CRO") industry, led by companies such as Covance, Inc., at http://www.covance.com; Parexel International Corporation, at http://www.parexel.com, and Quintiles Transnational, at http://www.quintiles.com. *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at note 30 and accompanying text. Nevertheless, academic institutions' embrace of industry relationships has heightened regulatory and ethical hurdles, including institutional conflicts. *See generally id.* For example, NIH concerns led to the demise of Boston University's plans to use Framingham Study data in genomics studies. *See* Vicki Brower, *Framingham Heart Study Genomics Firm Stops Beating*, BIOTECHNOLOGY NEWSWATCH, Jan. 15, 2001, p. 1., 2001 WL 8787439.

[149] Malinowski, *Snake Oil*, *supra* note 3, at 35-36 (stating that many medical community insiders think that "the use of predictive genetic testing with clinical utility for many common disorders is decades removed from the present realities of managed care.").

could add an additional dimension of complexity to drug prescribing.[150] 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 substitutes 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 classifications, cruder pharmaceuticals, and broad off-label use.

Pharmacogenetics also will have a profound impact on reimbursement decision-making and patient access, and set in motion a series of market changes presently difficult to fully define and measure.[151] Just a few decades ago, prescriptions generally cost less than $10, and a prescription charge of $100 would have caused patients, health care providers, and payers to balk. However, technology has elevated costs with capabilities.[152] Pharmacogenomics offers the potential of cost savings and human capital returns from improved health care outcomes.[153] Nevertheless, the precision resulting from meaningful pharmacogenomics suggests industry will have to recoup the costs of developing these innovative drugs from much smaller patient populations, meaning even higher drug costs for those who take the drugs.[154] Pharmacogenomics will also introduce new costs, including genetic profiling, data collection and processing, and monitoring services. Given the data collection gen-

[150] *See generally* GENETICS IN THE CLINIC, *supra* note 146; Lee M. Silver, *The Meaning of Genes and "Genetic Rights"* 40 JURIMETRICS 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 Abramowitz, *The Financial Impact of Genomics*, THE BOND BUYER, Dec. 13, 2000, p. 18, 2000 WL 30670701. *See also* Juma et. al., *supra* note 33.

[153] *See generally* Pincowish, *supra* note 50 and accompanying text.

[154] *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at n.21 (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. . . ."). *See also* Malinowski, *FDA Regulation*, *supra* note 20, 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.[155] 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.[156]

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.[157] Nevertheless, recent history is telling: biotechnology and genetic medicine have influenced the delivery of care in jolting ways over the last decade.[158] Therefore, in the context of pharmacogenomics, pragmatism mandates not assuming the luxury of time to resolve major law, business, and health care challenges associated with this technology. This article has identified many of

[155] Malinowski, *Snake Oil*, *supra* note 3, at 41. *See also* Milt Freudenheim & Melody Petersen, *The Drug-Price Express Runs into a Wall*, N.Y. TIMES, Dec. 23, 2001, at 1 (reporting that market resistance to new drugs in the absence of significant clinical utility offsets price increases).

[156] Presumably, the FDA will require precision labeling for drugs developed with heavy utilization of genetic profiling, and the FDA may even require genetic profiling as a pre-condition for approved market use. For a technical treatment of the FDA's review of new drugs and approval process, see MALINOWSKI, BIOTECHNOLOGY, *supra* note 88, at ch. 11.

[157] *See* Kahn, *supra* note 22, at 20; Freudenheim & Petersen, *Drug-Price Express*, *supra* note 155, at 1 (stating that the rise in health insurance premiums and an economic downturn has led to an unstable drug market). *Cf.* Malinowski, *Snake Oil*, *supra* note 3, at 47 (charting how current enabling techniques allow industry players to develop new research possibilities).

[158] 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.phrma.org (site of the Pharmaceutical Researchers and Manufacturers of America (PhRMA), the world's leading pharmaceutical trade organization); http://www.bio.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, *see* Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163, n. 1 (1996).

these challenges and emphasized that now is the time to address them.

A premise implied throughout this article is that those engaged in shaping health law, health policy, and bioethics must research and address the utilization of innovative technologies in the drug development pipeline and the transition of resulting technologies into the delivery of health care in a diligent manner.[159] Arguably, in many areas where law and science overlap, the long-standing divide between technology and responsive, fact-based, otherwise pragmatic, and intellectually thoughtful law and policy has widened into an abyss over the last decade or so.[160] Given the quickening pace of advances in contemporary life science through bioinformatics and other enabling technologies,[161] the divide between law and life science continues to widen in several now pressing areas and with increasingly dire health, economic, policy, and ethical consequences, thereby raising more complicated regulatory challenges.[162] A generation of unprecedented, often breakthrough, life science is now reaching delivery of care and entering a United States health care finance system that has been critiqued for decades for failing to guaranty a minimum standard of care for the U.S. population.[163] The number of uninsured and insufficiently insured has risen over the years to reach more than forty million Americans, and those ranks continue to expand and include more working Americans.[164] Moreover, accurately gauging the entry of specific scientific capabilities into health care application, especially under the expansive shadow cast by the unpredictability of advances in enabling

[159] *See* Malinowski, *Snake Oil*, *supra* note 3, at 39-41 (discussing "Shared Responsibility for Widening the Gap.").

[160] *See id.* at 39 (commenting that the Ethical, Legal, and Social Implications (ELSI) program of the HGP has overlooked the "systemic introduction of predictive genetic testing into health care").

[161] *See supra* Part I ("Traditional Pharmaceuticals and the Changing Pharmaceutical Economy").

[162] *See* Michael J. Malinowski, *Biotechnology in the USA: Responsive Regulation in the Life Science Industry*, 2 INT'L J. BIOTECHNOLOGY 16 (2000).

[163] *See generally* Richard D. Lamm, *Universal Health Care Coverage: A Two-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).

[164] *See* Arthur Jones, *Stretched to the Limit*, NAT'L CATH. REP., Feb. 22, 2002, at 3, 2002 WL 10828411 (explaining that there are approximately forty million uninsured/insufficiently insured citizens in the United States and that many of those joining the ranks of the uninsured are working Americans).

technologies,[165] is a Herculean task.[166] The present state of some areas of relevant law and scholarship suggest that the legal profession has yet to engage in a meaningful, ongoing dialogue with those pushing out the forefronts of life science R&D and directly engaged in health care innovation.[167]

[165] *See* Malinowski, *Snake Oil*, *supra* note 3, at 26 (describing how enabling technologies have had an explosive impact on biotechnology R&D—perhaps mostly to the surprise of the health care community).

[166] *See supra* note 22 and accompanying text.

[167] Patent law provides a pressing example, for intellectual property policy innately presumes insight about and sensitively towards markets, economic reality, and the actual practices of technology innovators. *Cf.* PHILIP W. GRUBB, PATENTS FOR CHEMICALS, PHARMACEUTICALS AND BIOTECHNOLOGY: FUNDAMENTALS OF GLOBAL LAW, PRACTICE AND STRATEGY (1999) [hereinafter "*Patents for Chemicals*"] (noting in the preface that "in the previous edition [of this treatise] a number of predictions were made, most of which turned out to be completely incorrect."). Arguably, the U.S. patent regime did not anticipate the jolting advances in the state of the art introduced by fields such as biotechnology, genomics, and bioinformatics over the last several years and, in hindsight, patent criteria may have been interpreted too broadly throughout the 1990s. The USPTO responded in January 2001 by issuing revised standards for written description and utility in genetics. *See* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1092-1099 (Jan. 5, 2001) (setting forth specific standards); Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, P1, "Written Description" Requirement, 66 Fed. Reg. 1099 (2001). Ideally, as concern about over patenting in biotechnology became a pressing topic in the early 1990s, law academia should have responded by undertaking pragmatic field work in the life science sectors, demonstrating appreciation for "real world" implications, and then setting forth insightful, sector-sensitive proposals to modify application of traditional patent criteria and practices while remaining faithful to these core criteria. Certainly, some of this work was done. *See, e.g.*, James Donahue, Note, *Patenting of Human DNA Sequences—Implications for Prenatal Genetic Testing*, 36 BRANDEIS J. FAM. L. 267, 282 (1997-1998). Nevertheless, even after former President Clinton and Prime Minister Tony Blair made statements on March 14, 2000 critical of biotechnology patenting that caused the biotechnology market sector to drop by $100 billion over the next 24 hours, some law academics have continued to fail to distinguish the information technology sector from the life science sector with meaningful sensitivity reflective of the obvious scientific, economic, and other "real world" differences. *See* Andrew Pollack, *Protecting A Favorable Image: Biotechnology Concerns in Quandary Over Drug Giants*, N.Y. TIMES, Apr. 4, 2000, at C1. *See also* Malinowski, *Snake Oil*, *supra* note 3, at n.22. For example, some have proposed transplanting cornerstone doctrine in copyright and trademark such as "fair use," a doctrine proven workable for the information technology and publishing sectors, into the body of patent jurisprudence. *See* Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 COLUM. L. REV. 1177, 1236-1237 (2000). While expansion of mechanisms already present in the patenting regime such as the reexamination procedure may prove desirable and even critical for the advancement of life science, analysis should embody understanding of and appreciation for the technical, pragmatic differences between life science R&D and other sectors that rely much more heavily on copyright and trademark protection. The extraordinary rate of failure, cost, time, and other risks—such as regulatory uncertainty and market unpredictability—associated with life science R&D readily distinguish the sector. *See* GRUBB, *supra* note 167, at 225-226 (highlighting the perspective of a European patent attorney with decades of practice experience in multiple, technology-driven sectors). As demonstrated in March 2000 and recognized by the National Institutes of Health in its August 2001 report, significantly

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 within health science institutions.[172]

weakening the patent regime would have dire consequences on the behavior of those who invest their careers—whether based in academia or industry—in pharmaceuticals, and presumably even more dire consequences for the patients and their families and friends who await their commercial development and availability. *See generally* DEP'T HEALTH & HUMAN SERVS., NAT'L INST. OF HEALTH, NIH RESPONSE TO THE CONFERENCE REPORT REQUEST FOR A PLAN TO ENSURE TAXPAYERS' INTERESTS ARE PROTECTED (July 2001), *available at* http://www.nih.gov/news/070101wyden.htm. *But see* Arti K. Rai, *The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost, & Access in the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 178-80 (2001) (proposing a curtailment of patent rights premised on cost savings attributable to use of pharmacogenomics).

[168] *See generally* Michael J. Malinowski, Symposium, *Conflicts of Interest in Clinical Research: Legal and Ethical Issues*, 8 WIDENER L. SYMP. J. 47 (2001); Malinowski, *Snake Oil*, *supra* note 3, at 41-46 (explaining his thesis in "A Proposal For Regulatory Reform").

[169] *See generally* Malinowski, *Snake Oil*, *supra* note 3, at 41.

[170] *See generally* Malinowski, *Institutional Conflicts*, *supra* note 4, at 69-73 (suggesting new changes in "Proposals for Reform").

[171] *Id.*

[172] *Id.*

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,[173] 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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[173] *See* Malinowski, *Institutional Conflicts*, *supra* note 4, at n.21; *see also* Malinowski, *FDA Regulation*, *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.

[177] Melody Petersen, *TV Ads Spur a Rise in Prescription Drug Sales*, N.Y. TIMES, Mar. 8, 2002, at C13. *Cf.* Malinowski, *Snake Oil*, *supra* note 3, at 34;

[178] For a thoughtful discussion of the complexities of using genetics in the clinic, *see generally* GENETICS IN THE CLINIC, *supra* note 145.

genetics in human health.[179] During the interim, law should be used to ensure that the basic tenets of health insurance, meaning pooling and disbursement of risks across the population, are adhered to. Sight must also not be lost of the fact that proliferation of understanding about human genetics, widespread genetic testing, and the resulting flow of information should make genetics a "wash" for the purposes of health insurance payers. Heavy utilization of pharmacogenomics in drug development, coupled with proactive regulatory, other law, and health policy reforms identified throughout this article, should quicken our transition through the awkward period of introduction and into the future of health care.

CONCLUSION

The complexities associated with commercialization of pharmacogenomics are extraordinary. This article has identified and discussed many of these complexities, including those associated with the changing pharmaceutical economy, trends in pharmaceutical R&D, and implications for the delivery of health care and the roles of patients, research subjects, and providers.

Nevertheless, pharmacogenomics introduces tremendous opportunities to improve health care, realize some immediate cost savings (for example, reducing the incidents of adverse reactions to pharmaceuticals), and increase human health and capital. Therefore, the legal, medical, and life science communities must rise to the challenge of working through the complexities associated with pharmacogenomics rather than continuing to assume the luxury of time or simply damning the endeavor and looking away.

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[179] *See* Malinowski, *Snake Oil*, *supra* note 3, at 33-41 (considering "The Consequences of Genetic Exceptionalism").