

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

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Introduction

Completion of maps of the human genome¹ and the explosive emergence of a multitude of complementary technologies ranging from DNA chips (commonly referred to as “biochips”)² to sophisticated software have transformed great expectations for genetic medicine into goals potentially obtainable in the foreseeable future.³ The pharmaceutical and biotechnology industries are utilizing genetics-based research to

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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 SCIENCE 1145 (February 16, 2001) (issue entitled “The Human Genome”); 409 NATURE 745 (Feb. 15, 2001) (issued dedicated to 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 is available at the Internet site of the National Human Genome Research Institute (NHGRI), available at www.nhgri.nih.gov (last visited Mar. 24, 2002).

² For 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 & tbl. B.1 (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 31-33 & app. tbl. 1 (2000). See generally Aris Persidis, *Biotechnology in a Snapshot*, 18 NATURE BIOTECHNOLOGY IT2 (2000) (Industry Trends Supplement). The technologies continues to evolve, and often in fundamental ways. For example, in March 2002, United States patent 6,355,420 was issued for a new methodology for sequencing DNA that mimics the way nature reads genetic information. See Teresa Riordan, *Patents: An Obsession with DNA and the Human Genome Leads to Development of a Technology*, N.Y. TIMES, Mar. 18, 2002, C2 (profiling the work of Dr. Eugene Chan, founder and chairman of U.S. Genomics).

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 As a consequence 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

⁴ Pharmacogenomics encompasses identification of cell function and the utilization of the predictability of cell function in response to chemical stimuli at the genetic level to drive drug development. *See* Malinowski, *Snake Oil*, *supra* note 3, at tbl. 2. This field is likely to accelerate drug discovery and introduce some clinical trials cost savings, but also to divide traditional disease classifications and shorten the market life span 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. SYMPOSIUM J. 47, n.21 (2001); Ronald Rosenberg, *Development of Drugs Seen Faster, Cheaper*, BOSTON GLOBE, June 5, 2001, at D1, D2, available at 2001 WL 3936608. *See also infra* note 17 and accompanying text; *infra* Part III.C.2 (“Health Care Provider Competency”). *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 Institutional Conflicts*, *supra* note 4, at n.21. *See generally Snake Oil*, *supra* note 3..

⁶ *See generally id.*

⁷ *See Francis Collins, Statement on Genetic Testing in the New Millennium: Advances, Standards, Implications Before the H.R. Subcommittee on Technology*, Committee on Science, 106th Cong., Apr. 21, 1999 (page number not available); Malinowski, *Snake Oil*, *supra* note 3, at 31-33 & tbl. 2; 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 & tbl. 2.

impact of genetic characteristics on the health care of individuals who possess the characteristic(s) at issue is a field known as pharmacogenetics.⁹

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

- 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 10,000 or more drug targets for use in developing potentially tens of thousands of drugs;¹⁰
- Intense demand for human biological samples and access to pedigree and family history;¹¹
- Multiplication of the number of clinical trials and increased participation in trials;¹²
- More direct communication between human subjects and trial sponsors and investigators via Internet compilation and public dissemination of clinical trial information;¹³
- 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

⁹ *Id.* at tbl. 2. See also Sharon Begley, *Made-to-Order-Medicine*, NEWSWEEK, June 25, 2001, at 64.

¹⁰ See PHARMACEUTICAL INDUSTRY PROFILE 2001: A CENTURY OF PROGRESS 14 (2001), available at www.phrma.org; PHRMA, THE PHARMACEUTICAL INDUSTRY PROFILE v 2000 (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* note 84 and accompanying text.

¹⁴ See *infra* Part IV (“Proposals for Legislative and Regulatory Reform”). See generally Michael J. Malinowski, *Institutional Conflicts and Responsibilities in an Age of Academic-Industry Alliances*, 8 WIDENER L. SYMPOSIUM J. 47, 69-73 (2001) (proposals for regulatory reform).

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

- Heightened medical privacy concerns attributable to the fact that exponentially more genetic information will be obtainable from individual samples;¹⁶
- Fracturing of tradition disease classifications and recognition of health conditions not yet fully identified;¹⁷
- Increased specificity in FDA drug labeling and restrictions on approved uses;¹⁸
- 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
- 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;²⁰ and
- As a consequence of a jolting rise in the prices of breakthrough new drugs, greater public and political support for price controls on pharmaceuticals.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

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 155 and accompanying text.

¹⁹ See *infra* Part III.C.3 (“Market Acceptance and Patient Access”).

²⁰ See Malinowski, *Institutional Conflicts*, *supra* note 14, 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).

²¹ This sentiment in favor of price controls on pharmaceuticals was strong enough to prompt the National Institutes 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 Runs Into a Wall*, N.Y. TIMES, Dec. 23, 2001, at 1, 13 (reporting market resistance to new drugs in the absence of significant clinical utility benefits to offset price increases).

profiling. Part III probes implications for the delivery of health care and the roles of patients, research subjects, and providers, including pharmacists. Part IV introduces proposals for responsive reform.

Part I: Traditional Pharmaceuticals and the Changing Pharmaceutical Economy

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

²² See Malinowski, *FDA Regulation*, *supra* note 20, at 224-25. See generally BOSTON CONSULTING GROUP, *THE PHARMACEUTICAL INDUSTRY INTO ITS SECOND CENTURY: FROM SERENDIPITY TO STRATEGY* (Jan. 1999); See Virginia Munger Kahn, *Managers Say this Decade Belongs to Health Care*, N.Y. TIMES, Jan. 6, 2002, at 20.

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 improved version, 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 ROBINS-ROTH, *supra* note 2, 164-165, tbl. 20.1.

²⁴ See *id.*

²⁵ For example, in December 2001, 29 attorneys general filed suit against Bristol-Myers Squibb to break the company's market hold over Buspar, an anti-anxiety drug. See Kahn, *Managers Say*, *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 several independent lawsuits against pharmaceutical makers. This suits are based upon allegations that the companies have inflated drug prices, and most involve allegations that the defendants have 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* ch. 19, 391-392 (Jeffrey S. Lubbers ed., ABA 2002).

especially in an age of intense controversy over drug pricing.²⁶ Under the Hatch-Waxman Act,²⁷ generic competitors are able to enter the marketplace via an Amended New Drug Application (“ANDA”) by establishing bioequivalence²⁸ with approved products, rather than undertaking the more burdensome task of establishing fundamental safety and efficacy.²⁹ Generic manufacturers thereby have the opportunity to enter the market without incurring the hundreds of millions of dollars in R&D costs—for example, the costs associated with generating and processing often voluminous Phase I through Phase III clinical data to establish safety and efficacy for market approval, and then follow-on studies (“Phase IV data”)—and without assuming the enormous risks and time-consuming market development challenges undertaken by drug innovators.³⁰

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”),³¹ longstanding

²⁶ See Generic Pharmaceutical Association (GPhA), at www.gphaonline.org (represents more than 90% of the nation’s generic pharmaceutical industry based upon sales).

²⁷ 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 (2000).

²⁸ “Bioequivalence” is equivalence in bioavailability, meaning 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.

²⁹ 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, 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.

³⁰ See *infra* note 29. See also MICHAEL J. MALINOWSKI, *BIOTECHNOLOGY LAW, BUSINESS, & REGULATION* ch. 11 (Aspen Law & Business 1999 & Supps. 2001, 2002).

³¹ 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

seams among these global markets continue to unravel. Although the United States may remain optimistic about the promise of fully implementing GATT/TRIPS by 2005 even among signatories with developing economies, daunting challenges to global harmonization continue to arise.³² 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 an aggressive form of breast cancer,³³ Cerezyme for Gaucher's disease,³⁴ Pulmozyme for cystic fibrosis,³⁵ and protease inhibitors for AIDS patients³⁶ are juxtaposed with the proliferation of deaths in developing economies from highly preventable and treatable conditions such as basic

Uruguay Round, vol. 31, 33 I.L.M. 81 (1994), reprinted in MICHAEL J. MALINOWSKI, BIOTECHNOLOGY: LAW, BUSINESS, & REGULATION app. (1999 & supps. 2001, 2002).

³² See generally CTR. FOR INT'L DEV. AT HARVARD UNIV., GLOBAL GOVERNANCE OF TECHNOLOGY: MEETING THE NEEDS OF DEVELOPING COUNTRIES, SYNTHESIS REPORT (June 2001), at http://www.cid.harvard.edu/cidbiotech/globalgovconf/report_abstract.htm (last visited Oct. 12, 2001) [hereinafter "CID site"]; Jeffrey D. Sachs, *Balms for the Poor*, THE ECONOMIST, Aug. 14, 1999.

³³ 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, 2001 WL 21128992 (page number unavailable online).

³⁴ 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, 2001 WL 6617162.

³⁵ Information about Pulmozyme may be obtained from its manufacturer, Genentech, Inc. of South San Francisco, at www.genentech.com. See J.D. Kleinke, *The Price of Progress: Prescription Drugs in the Health Care Market*, Sept. 1, 2001, p. 4360, 2001 WL 10696964 (included in a category of expensive new drugs that lower short-term health care costs but guaranty higher costs in the long run—"the economics of smoking in reverse").

³⁶ A year's therapy in the United States costs approximately \$8,000. See *Latest Developments in HIV Diagnosis and Treatment*, PULSE, p. 60, Feb. 11, 2002, 2002 WL 13571781 (no author identified).

nutrition deficiencies³⁷ and malaria.³⁸ 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.³⁹ 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 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.⁴⁰ The leading AIDS drug manufacturers within the pharmaceutical industry have made major concessions but been unable to completely fend off generic competitors.⁴¹

³⁷ 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 deficiencies. See David Lague, *Biotechnology*, FAR. E. ECON. REV., Apr. 4, 2002, p. 34, 2002 WL-FEER 5169787.

³⁸ “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).” Editorial, *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 Sec. Thompson to Visit Africa*, ASSOCIATED PRESS, Mar. 29, 2002, 2002 WL 17189950 (page numbers unavailable online); Bill Gates, *Bono Call on Leaders at World Economic Forum*, M2 PRESSWIRE, Feb. 1, 2002, 2002 WL 4158486 (no author identified, and page numbers unavailable online).

³⁹ “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, 2002 WL 17725854 (no author identified and page numbers unavailable). See Vidyut Kumar Tu, *WHO Theme—Stop TB, Fight Poverty*, TIMES INDIA, Mar. 30, 2002, 2002 WL 17726586 (page numbers unavailable).

⁴⁰ See CID site, *supra* note 32; Donald G. McNeil Jr., *New List of Safe AIDS Drugs*, N.Y. TIMES, Mar. 21, 2002, 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.”).

⁴¹ See McNeil, *supra* note 40, at A3.

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.⁴² The absence of meaningful life science capabilities in many biodiverse areas of the world raises global susceptibility to public health challenges.⁴³

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.⁴⁴ The overall revenue allocated to R&D has risen from 11 to 20.3 percent over the last 20 years,⁴⁵ and overall pharmaceutical investment in R&D has risen from approximately \$2 billion in 1991 to \$30.5 billion in 2001.⁴⁶

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

⁴² Cf. CID site, *supra* note 32; Donald G. McNeil Jr., *New List of Safe AIDS Drugs*, N.Y. TIMES, Mar. 21, 2002, A3. For those of us 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 gap between developed and developing economies.

⁴³ See generally LAURIE GARRETT, *THE COMING PLAGUE* (1994); JUDITH MILLER, STEPHEN ENGELBERG, WILLIAM BROAD, *GERMS: BIOLOGICAL WEAPONS AND AMERICA'S SECRET WAR* (2001); Sachs, *supra* note 32.

⁴⁴ See *supra* note 29. See also Malinowski, *Institutional Conflicts*, *supra* note 4, at 48-49.

⁴⁵ See PHRMA, 2001, *supra* note 10, at ch. 2; see also *supra* note 29.

⁴⁶ See *id.*

and products that generate billion-dollar revenue streams on an annual basis.⁴⁷ 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.⁴⁸

Part II: Trends in Pharmaceutical R&D

Traditional pharmaceuticals are understood largely based upon use in human subjects and patients—meaning clinical trial and physician experiences indicating that the compounds alleviate and/or ameliorate symptoms associated with particular diseases.⁴⁹

There is wide variation in patient responsiveness for most pharmaceuticals, ranging from nonresponsiveness to severe adverse events from the standard of care dosage.

Consequentially,

- 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;⁵⁰
- Our aging population now is testing the limit of our knowledge about drug combinations and interactions;⁵¹

⁴⁷ See 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); Malinowski, *Institutional Conflicts*, *supra* note 14, at n.21. See generally BOSTON CONSULTING GROUP, *supra* note 22.

⁴⁸ See *infra* notes 148-151 and accompanying text.

⁴⁹ See generally BOSTON CONSULTING GROUP, *supra* note 22; PHARMACEUTICAL INDUSTRY PROFILE 2001, *supra* note 10.

⁵⁰ *Companies Balance Risks, Rewards of Off-Labeling*, FOOD & DRUG LETTER, Mar. 15, 2002, 200 WL 12321164 (page numbers unavailable).

⁵¹ *More Seniors Hospitalized for Adverse Drug Reactions*, LETHBRIDGE HERALD, July 3, 2001, 2001 WL 22404622 (page numbers unavailable); Mary Desmond Pinkowish, *Prescribing for Older Patients: 5 Points to Remember*, PATIENT CARE, p. 45, 2000 WL 100711936 (Aug. 15, 2000).

- Dosage and drug combinations raise patient-by-patient challenges for physicians;⁵²
- Estimates for the health care costs associated with unintended reactions to pharmaceuticals have reached as much as \$100 billion annually;⁵³ and
- Many prevalent diseases remain untreatable with traditional pharmaceuticals.⁵⁴

However, times are changing. Through fields such as genomics (identifying genes and gene function),⁵⁵ proteomics (identifying protein function),⁵⁶ and bioinformatics (the combination of biotechnology and information technology),⁵⁷ the pharmaceutical industry anticipates churning vast amounts of data from voluminous numbers of samples and identifying as many as 10,000 drug targets over the next several years.⁵⁸ This expectation is premised upon new sets of tools for discovering, mapping, and modifying

⁵² *Id.*

⁵³ Although the reliability of the Institutes of Medicine's 1999 report has been called into question (available at www.IOM.gov), 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, 2002 WL 16980099 (no author identified). See David Brown, WASH. POST, Mar. 26, 2002, F01, 2002 WL 17585639. The problem also is pervasive outside of the United States. See 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 prescribing and administering medications).

⁵⁴ 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 still remain formidable challenges. Heart disease is responsible for 33% of all deaths among those 65 and older, and cancer is responsible for 22% of the deaths in this age group. Christine Himes, *Elderly Americans*, POPULATION BULLETIN, Dec. 1, 2001, p. 3, 2001 WL 29421290.

⁵⁵ Malinowski, *Snake Oil*, *supra* note 3, at tbl. 1.

⁵⁶ Malinowski, *Snake Oil*, *supra* note 3, at tbl. 2. IBM's Blue Gene can identify (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, 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.

⁵⁷ Malinowski, *Snake Oil*, *supra* note 3, at tbl. 1.

⁵⁸ 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. PHARMA, INDUSTRY PROFILE 2000, *supra* note 10, at v.

genetic information—meaning tools for distinguishing gene expression and isolating which particular genes to study.⁵⁹ Utilization of DNA chips, which are silicon chips embedded with multiple, distinguishable bits of DNA has made large-scale screening possible.⁶⁰ DNA chips can be used to test the samples of individuals for the presence of thousands of identified genetic variations and, alternatively, to screen hundreds of thousands of individuals with a shared phenotype characteristic to isolate and identify shared genetic expression. This technology has made it feasible to do comprehensive gene expression comparisons among large groups of people—e.g., a well-documented disease group such as the Framingham heart study patients, or even the population of a Iceland. In fact, bioinformatics capabilities have inspired the formation of a consortium among pharmaceutical, biotech, and academic participants to compile data on the impact of variations of single nucleotide polymorphisms, 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

⁵⁹ See generally Malinowski, *Snake Oil*, *supra* note 3; PhRMA, *INDUSTRY PROFILE 2001*, *supra* note 10; BOSTON CONSULTING GROUP, *supra* note 22.

⁶⁰ 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, *ALCHEMY*, *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). *Snake Oil*, *supra* note __, at 32. Affymetrix has anticipated introducing a commercial chip with the capacity to screen for 400,000+ arrays by 2003. ROBBINS-ROTH, *ALCHEMY*, *supra* note 2, at 73-81 & tbl. B.1.

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.

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 shadowing the advancement of contemporary life science and, in turn, industry is financing and advancing this field of science—thereby moving us into an era of genetic precision in pharmaceutical development and prescription drug delivery.⁶³ Consequentially, genetic testing is entering the medical setting as an accompaniment to drug delivery.⁶⁴ For example, in 1998, Genentech, Inc. 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 Her2-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

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 76. Patent applications for biotechnology, organic chemistry, and pharmaceuticals have nearly doubled from 1996 to 2000 (reaching 32,705 in 2000), and approximately 2-3rds 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. *Annual Reports: 1999, supra*.

⁶³ See generally Malinowski, *Snake Oil*, *supra* note 3; PhRMA, *INDUSTRY PROFILE 2001*, *supra* note 10; PhRMA, *INDUSTRY PROFILE 2000*, *supra* note 10.

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

⁶⁵ See generally ROBERT BAZELL, *HER2: THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER* 29-53 (1998).

making 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. government-headed initiative in a race to map the human genome,⁷² Craig Venter stated that the ultimate Celera consumer would be the individual who will access the company's databases to get information about his or herself and make more informed health care decisions.⁷³ Some companies already have moved forward with business

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 n.31.

⁶⁷ See 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*, SAN FRANCISCO CHRON., Feb. 10, 2002, G1, at 2002 WL 4012496.

⁶⁸ See *id.*

⁶⁹ See generally Malinowski, *Snake Oil*, *supra* note 3,

⁷⁰ See *id.* at 32-33 (providing citations).

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, 2002 WL5145033 (page numbers unavailable).

⁷² See *supra* note 1.

⁷³ Fisher, 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.

plans premised upon genetic profiling and direct-to-consumer interaction. For example, in summer 2000, DNA Sciences launched a Web site to recruit people to donate their DNA to help identify genetic variations that cause disease, thereby compiling the database gene trust, a large statistical sample.⁷⁴ In December 2000, DNA Sciences acquired PPGx, which had announced plans in fall 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

Part 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 10,000+ drug targets⁷⁷ 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 diversity with the human species is

⁷⁴ DNA Sciences, at <http://www.dna.com>

⁷⁵ *DNA Sciences Inc.*, MED AD NEWS, Aug. 1, 2001, p. 16, 2001 WL 26968874 (no author identified).

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

⁷⁷ See *supra* note 10 and accompanying text.

attributable to a mere .1 percent of DNA.⁷⁸ However, in March 2001, the science community determined that the human genome consists of approximately 30,000 genes rather than the 80,000 to 150,000 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 history,⁸¹ intensified commercial pressures on both industry and academia in a 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

⁷⁸ See 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*, HOUSTON CHRON., Mar. 23, 2001, p. 1, 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.

⁸¹ See *infra* section III.A.1.

⁸² See *infra* sections III.A.2. and III.A.3.

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 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 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. One such question is whether the Common Rule⁸⁸ will be

⁸³ See *infra* section III.B.

⁸⁴ See *infra* note 124 and accompanying text (identification of web sites that make clinical trial information directly accessible by the general public).

⁸⁵ See generally *supra* notes 55-68 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 technical discussion about human subject protection regulations and their implementation, see MALINOWSKI, BIOTECHNOLOGY, *supra* note 31, at ch. 9; see generally PRICEWATERHOUSE COOPERS, LLP, INSTITUTIONAL REFERENCE BOARD (IRB) REFERENCE BOOK (Michele K. Russell-Einhorn & Thomas Puglisi, eds., 2001).

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

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 In March 2002, the Bush Administration discarded the HIPAA

⁸⁹ U.S.C. 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) (proposing establishment of a 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 *id.* The primary regulatory issue is whether encrypted human biological samples will be treated as the equivalent of identifiable samples and therefore 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 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>. See generally MALINOWSKI, *supra* note 88; IRB REFERENCE BOOK, *supra* note 88.

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 (no author identified and page numbers unavailable).

⁹³ Examples of these commercial suppliers include The First Genetic Trust, www.firstgenetic.net, and Genomics Collaborative, Inc., www.dnarepository.com. See Jeffrey Krasner, *Gene Pooling: Company Builds World’s Largest Library of Genetic Material*, BOSTON GLOBE, Aug. 22, 2001, at F1, F4. 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. See NBAC, *Ethical and Policy Issues*, *supra* note 90. In addition to commercial suppliers, some teaching hospitals are compiling central tissue banks with contemporary

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 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

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 *supra* note 92.

⁹⁵ See *supra* note 29 (PhRMA estimates that during the 1990s the time required to develop a new drug stretched to more than 14 years).

⁹⁶ See *infra* section III.A.2 (“Protection of Human Subjects”). 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 92.

⁹⁷ See Generally NBAC REPORT , HUMAN BIOLOGICAL SAMPLES, *supra* note 90.

⁹⁸ Physicians may be paid “reimbursement” fees of thousands of dollars per patient. See Malinowski, *Institutional Conflicts*, *supra* note 4, at n.94. See generally Francis H. Miller, *Trusting Doctors: Tricky Business When It Comes to Clinical Research*, 81 B.U. L. REV. 423 (2001).

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>

breakthrough drugs to offset the loss of billion-dollar revenues due to patent expirations has heightened over the last few years, and that pressure continues to rise.¹⁰⁰

The United States' framework to protect human subjects and complementary agency policies and enforcement practices¹⁰¹ generally 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

(details on approximately 5,500 mostly government-funded clinical trials); <http://cancertrials.nci.nih.gov> (the National Cancer Institute's clinical trial listing); <http://actis.org> (the AIDS clinical trials information service (ACTIS)); <http://www.veritasmedicine.com> (lists trials and standard treatments for numerous diseases); <http://www.americasdoctor.com/clintrials/main.cfm> (trials in seven disease categories, excluding cancer); and <http://www.acurian.com/patient> (developing lists of trials in various disease categories).

¹⁰⁰ See *supra* note 23-24 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.

¹⁰² See generally Malinowski, *Institutional Conflicts*, *supra* note 14.

¹⁰³ See *id.* at 56-66.

¹⁰⁴ See generally Mildred K. Cho et al., *Policies on Faculty Conflicts of Interest at US Universities*, 284 JAMA 2203 (2000) (reporting on an empirical survey indicating that the vast majority of research institutions have failed to establish relevant policies).

¹⁰⁵ See generally Malinowski, *Institutional Conflicts*, *supra* note 14.

research.¹⁰⁶ In May 2001, the National Bioethics Advisory Commission (“NBAC”) proposed establishing of single, independent office with jurisdiction over all (privately-funded, as well as federally-funded) domestic human subjects research and a single set of rules.¹⁰⁷ Similarly, Dr. Greg Koski, Director of the Office for Human Research Protections (OHRP) in HHS, called for the introduction of universal standards for IRBs.¹⁰⁸

Under the Bush Administration, the FDA and NIH still await leadership. Although President Bush has established a new Council in Bioethics, thus far, this commission has fixated on the issue of human cloning.¹⁰⁹ Nevertheless, research continues to rage onward, and with increased utilization of genetic profiling.¹¹⁰ Never have as many clinical trials been underway, and pharmacogenomics is being embraced in clinical research to streamline both costs and time.¹¹¹ 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

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>; Donna Shalala, *Protecting Human Subjects—What Must Be Done*, 343 NEW ENG. J. MED. 808, 809 (2000).

¹⁰⁷ National Bioethics Advisory Commission, *Recommendations: Ethical and Policy Issues in Research Involving Human Participants* (May 18, 2001) (proposing establishment of a single, independent federal office to implement a unified, single set of regulations and guidance), *available at* <http://bioethics.gov/press/finalrecomm5-18.html>.

¹⁰⁸ See DHHS, <http://ohrp.osophs.dhhs.gov/> (Internet site of the Office for Human Research Protections).

¹⁰⁹ The President’s Council on Bioethics, <http://bioethics.gov/>.

¹¹⁰ See generally Malinowski, *Snake Oil*, *supra* note 3. See also *supra* Part II.

¹¹¹ Malinowski, *Institutional Conflicts*, *supra* note 14, at n.1; Malinowski, *Snake Oil*, *supra* note 3, at 31-33. See also Ann M. Thayer, *BioInformatics for the Masses*, CHEMICAL & ENGINEERING NEWS, Feb. 7, 2000, at 19; Julia Burguslavsky, *Pharma to Transform by 2005*, DRUG DISCOVERY & DEVELOPMENT, Sept. 1999, at 71.

has triggered considerable anxiety over human subject participation,¹¹² and the joint venture in Japan by Variagenics and Covance in November 2000.¹¹³ Similarly, Iceland's DeCode Genetics, which has collaborations with several U.S. interests, has established Encode, a subsidiary specializing in pharmacogenomics studies.¹¹⁴

3. Conflicts of Interest

The U.S. regulatory regime to contain conflicts of interest—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.¹¹⁵ Trust is a questionable assurance mechanism to police researchers and institutions exposed to commercial incentives such as royalty and equity interests.¹¹⁶ 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:

¹¹² See John Pomfret, *Harvard Rebukes Head of China Gene Study*, WASH. POST, Aug. 9, 2001, A14, 2001 WL 23185560.

¹¹³ See *Covance Eyes Pharmacogenomics Business in Japan*, CHEMICAL BUS. NEWS BASE, Nov. 24, 2000, p. 12, Nov. 24, 2000, 2000 WL 28797530 (no author identified).

¹¹⁴ Decode Genetics, Inc., www.decode.com. DeCode also has established DeCode Cancer to commercialize diagnostics and therapeutics. See *id.*

¹¹⁵ Federal thresholds have been established by the Department of Health and Human Services (DHHS), National Institutes of Health (NIH) to define “significant financial interest.” According to NIH, a “significant financial interest” is an “equity ownership in companies exceeding 5%, and/or aggregate payments received from companies in excess of \$10,000/year.” See 42 C.F.R. § 50.603(1), (3)-(5) (2000); 21 C.F.R. §§ 54.1-54.6 (2001). See Malinowski, *Institutional Conflicts*, *supra* note 14, at 78-80 and accompanying text (addressing both NIH and FDA guidelines). Nevertheless, deference is shown to institutions to manage conflicts of interest, and heavy reliance is placed upon institutions to manage them. See generally Malinowski, *Institutional Conflicts*, *supra* note 14.

¹¹⁶ See generally Malinowski, *Institutional Conflicts*, *supra* note 14.

“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.”¹¹⁷

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 animal studies,¹¹⁸ instances of doctors enrolling and treating patients in clinical studies paid for by the companies they own,¹¹⁹ disputes between academics and their industry sponsors over data,¹²⁰ and pressures on universities to

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

¹¹⁸ 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 in companies sponsoring the trials they run, 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 a policy on conflicts of interest calling on all medical centers to develop guidelines embodying stipulations to avoid perceived as well as 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/ama/pub/category/2503.html>; Malinowski, *Institutional Conflicts*, *supra* note 14, at 70.

¹¹⁹ See Gelsinger Complaint, *supra* note 118. According to FDA, at least prior to the death of Jesse Gelsinger, this practice was becoming increasingly pervasive in the field of gene therapy in particular. Sheryl Gay Stolberg, *Biomedicine Is Receiving New Scrutiny as Scientists Become Entrepreneurs*, *NY TIMES*, Feb. 20, 2000, sec. 1, p. 26, col. 1.

¹²⁰ For example, 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 BIOTECH* 1235 (Dec. 2000).

loosen conflict-of-interest rules.¹²¹ In the absence of significant regulatory reform, escalating commercial pressures will increase risks to human subjects and research integrity.¹²²

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.¹²³ Clinical research has entered an era of transparency, meaning that information about clinical trials is on-line and accessible to the general public, and the public is seeking access.¹²⁴ As breakthrough treatments for presently untreatable conditions mature in the drug development pipeline, both patients and providers will more readily look to clinical trials for health care options.¹²⁵ 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.¹²⁶

¹²¹ Harvard University even considered lessening its relatively strict standards, but then decided not to. See Katherine Mangan, *Harvard Medical School Will Keep Its Conflict-of-Interest Policies*, CHRON. HIGHER EDUC., June 9, 2000, A36. 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.

¹²² See generally Malinowski, *Institutional Conflicts*, *supra* note 14. See generally *infra* Part IV.

¹²³ See Malinowski, *Institutional Conflicts*, *supra* note 14, at 53-56.

¹²⁴ This transparency is attributable in part to the United States' official, FDA-managed clinical trial web site, at www.clinicaltrials.gov. For additional clinical trial web sites, see *supra* note 99.

¹²⁵ See Malinowski, *Institutional Conflicts*, *supra* note 14, at 53-56.

¹²⁶ HEALTH CARE FINANCING ADMIN., MEDICARE COVERED 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>. See also

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 idiosyncracies may be decades removed. Nevertheless, market introduction of genetic tests to make prescription drug choices witnessed thus far is simply a glimpse into a foreseeable future.¹²⁷ Pharmacogenomics¹²⁸ as a R&D methodology will bring forth meaningful pharmacogenetics¹²⁹ 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.¹³⁰ 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.¹³¹ Such databases and services are presently available to members of the research community, and the mission of the ongoing work of the well-financed and

Malinowski, *Institutional Conflicts*, *supra* note 14, at 55-56. *See generally* SUSAN QUINN, HUMAN TRIALS: SCIENTISTS, INVESTORS, AND PATIENTS IN THE QUEST FOR A CURE (Perseus 2001) (a case study of the company AutoImmune that emphasizes the impact of clinical trials on patients awaiting innovative treatments and raises a series of ethical issues).

¹²⁷ Genetic profiling as an accompaniment to drug delivery is made tangible by present applications of such technology. *See supra* notes 65-68 and accompanying text.

¹²⁸ *See supra* notes 4-5 and accompanying text.

¹²⁹ *See supra* note 9 and accompanying text.

¹³⁰ *See supra* note 8 and accompanying text.

¹³¹ *See supra* notes 75-76 and accompanying text.

diligent SNP consortium is to churn out a voluminous number of genotype-phenotype (genetic-physical characteristic) connections.¹³²

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.¹³³ However, predictive genetic tests performed by their manufactures and made available to others as a service, which are known as “homebrew tests,” escape FDA regulation and arguably are not meaningfully regulated otherwise.¹³⁴

This regulatory exceptionalism was made all-too-clear in 1996-1997 when several biotech companies engaged in commercialization of predictive genetic tests for breast cancer premised upon links between the disease and BRCA1 and BRCA2 variations, but without data to establish clinical utility of this connection for women in general.¹³⁵

¹³² See The SNP Consortium Ltd., at <http://snp.cshl.org>. See also Malinowski, *Snake Oil*, *supra* note 3, at 32-33.

¹³³ 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.

¹³⁴ See Malinowski, *Snake Oil*, *supra* note 3, at 36, 43-44. See generally Amy Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555 (1998). The only meaningful federal oversight of homebrew testing is under the Clinical Laboratory Improvement Amendment regulations (CLIA), the scope of which is limited to regulating the proficiency/accuracy of testing and administrative requirements. See Genetic Testing Under the Clinical Laboratory Improvement Amendments, 65 Fed. Reg. 25,928 (May 4, 2000); 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), PRELIMINARY RECOMMENDATIONS ON THE ADEQUACY OF OVERSIGHT OF GENETIC TESTS 3-6 (2000). CLIA does not address clinical utility. See *id.*

¹³⁵ See Malinowski, *Snake Oil*, *supra* note 3, at 35-36.

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.¹³⁶ 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.¹³⁷ Especially given that most genetic tests have multiple potential uses,¹³⁸ definitional ambiguity is prevalent in this legislation.¹³⁹ 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.¹⁴⁰

2. Health Care Provider Competency

¹³⁶ *See id.*

¹³⁷ *See id.* In the midst of a series of federal legislative and administrative initiatives, states enacted an entanglement of genetics legislation. *See id.* at 36. For a concise, organized overview of the kinds of legislation states have enacted, *see* William F. Mulholland, I & Ami S. Jaeger, *Genetic Privacy and Discrimination: A Survey of State Legislation*, 39 JURIMETRICS 317-26 (1999). The actions most often prohibited 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, or 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. *See id.* at 317; Malinowski, *Snake Oil*, *supra* note 3, at 56.

¹³⁸ Malinowski, *Snake Oil*, *supra* note 3, at n.24 and accompanying text. Consider that a genetic test for over-expression of her-2-neu could be used: (1) in a woman with breast cancer to determine whether she should consider taking 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 Herceptin as a preventive measure, (3) or perhaps by a potential mother with a family history of breast cancer to screen embryos before undergoing in vitro fertilization.

¹³⁹ *Id.* at 28-31.

¹⁴⁰ *See generally id.*

The transition from fee-for-service into managed care has imposed time and other commercial pressures on the United States health care community.¹⁴¹ Even prior to 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.¹⁴² The explosive advancement of biotechnology from the research bench into the market has validated many of these concerns.¹⁴³ “In light of the towering and still rising wave of information, the all-knowing general practitioner is not a contemporary possibility.”¹⁴⁴

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.¹⁴⁵ 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

¹⁴¹ See generally *Capitation, Advances in Medical Technology, and the Advent of a New Era in Medical Ethics*, 22 AM. J.L. & MED. 335 (1996 symposium), reprinted in *TAKING SIDES: CLASHING VIEWS ON CONTROVERSIAL BIOETHICAL ISSUES* (Carol Levine ed., 7th ed. 1997).

¹⁴² Michael J. Malinowski & Robin J.R. Blatt, *Commercialization of Genetic Testing Services: The FDA < Market Forces, and Biological Tarot Cards*, 71 TULANE L. REV. 1211, 1245-1247 (1997).

¹⁴³ See Michael J. Malinowski, *Foreword: Academic-Industry Collaborations in the Clinic*, 8 WIDENER L. SYMPOSIUM J. ii, ii-iii & nn. 1-7 (2001).

¹⁴⁴ Malinowski, *Institutional Conflicts*, *supra* note 3, at 54.

¹⁴⁵ 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).

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 assuming an expanded role in the health care process.

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.¹⁴⁶ 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 the institutions are embracing technology transfer which may reach into clinical trials.¹⁴⁷

Nevertheless, many in the medical community are more familiar with the confidentiality, privacy, and potential discrimination issues associated with predictive

¹⁴⁶ See *supra* notes 69-76 and accompanying text (identifying some emerging Internet services, including genetic screening services to improve drug reactions and identify potential problems from drug interactions).

¹⁴⁷ See Liz Kowalczyk, *Profits and Costs*, BOSTON SUNDAY GLOBE, Mar. 24, 2002, at C1, C6. (“[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 Kowalczyk, *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 among Harvard and four other medical schools to counter private industry efforts to take over too much 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 3, 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 Bower, *Framingham Heart Study Genomics Firm Stops Beating*, BIOTECHNOLOGY NEWSWATCH, Jan. 15, 2001, p. 1., 2001 WL 8787439.

genetic testing than the technology itself.¹⁴⁸ 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 could add an additional dimension of complexity to drug prescribing.¹⁴⁹ The dangers of over-reliance on genetic profiling include over and under dosing, and false assurances that lead to failures to closely monitor drug interactions and to make necessary dosage adjustments and drug substitutes over time. In addition, the significant streamlining of clinical trials may heighten provider dependence on Phase IV data compiled in an ongoing manner 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.¹⁵⁰ 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

¹⁴⁸ Malinowski, *Snake Oil*, *supra* note 3, at 33-41.

¹⁴⁹ See generally GENETICS IN THE CLINIC, *supra* note 145; Lee M. Silver, *The Meaning of Genes and "Genetic Rights,"* 40 JURIMETRICS J. 9 (1999).

¹⁵⁰ See *infra* Part IV; see *supra* Part III. See generally Kahn, *Managers Say*, *supra* note 22, at 20 (identifying a number of market variables that bear upon the market performance of the biotechnology and pharmaceuticals sectors).

capabilities.¹⁵¹ Pharmacogenomics offers the potential of cost savings and human capital returns from improved health care outcomes.¹⁵² 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.¹⁵³ Pharmacogenomics also will introduce new costs, including genetic profiling, data collection and processing, and monitoring services. Given data collection generated by market use and the dynamic nature of the human genome in response to environmental stimuli, including pharmaceuticals as reflected in the need to make dosage and drug changes over time, the latter cost could prove significant.

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

¹⁵¹ 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, *Medical Technology*, THE BOND BUYER, Dec. 13, 2000, p. 18, 2000 WL 30670701. See also *supra* note 33.

¹⁵² See *supra* note 53.

¹⁵³ See Malinowski, *Institutional Conflicts*, *supra* note 14, at n.21; Michael J. Malinowski, *FDA Regulation of Biotechnology*, *supra* note 20, at 224.

¹⁵⁴ See 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, 13 (reporting market resistance to new drugs in the absence of significant clinical utility benefits to offset price increases).

utility of the pharmaceuticals developed with pharmacogenomics that carry widespread genetic profiling into the marketplace.¹⁵⁵

Part IV: Proposals for Legislative and Regulatory Reform

Admittedly, today's life science enabling technologies and commercial investment in applying those technologies make gauging tomorrow's health care a speculative endeavor even for experts.¹⁵⁶ Nevertheless, recent history is telling: Biotechnology and genetic medicine have impacted the delivery of care in jolting ways over the last decade.¹⁵⁷ 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 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.¹⁵⁸ Arguably, in many areas where

¹⁵⁵ Presumably the Food and Drug Administration (FDA) will require the labeling for drugs developed with heavy utilization of genetic profiling to reflect this precision, 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.

¹⁵⁶ See Kahn, *Managers Say*, *supra* note 22, at 20; Freudenheim & Petersen, *Drug-Price Express*, *supra* note 154, at 1, 13. Cf. Malinowski, *Snake Oil*, *supra* note 3.

¹⁵⁷ 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 for 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, app. 1 (1996).

¹⁵⁸ See Malinowski, *Snake Oil*, *supra* note 3, at 39-41 ("Shared Responsibility for Widening the Gap").

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.¹⁵⁹ Given the quickening pace of advances in contemporary life science through bioinformatics and other enabling technologies,¹⁶⁰ the divide between law and life science continues to widen in several now pressing areas and with increasingly dire human health, economic, policy, and ethical consequences—thereby raising increasingly complicated regulatory challenges.¹⁶¹ A generation of unprecedented, often breakthrough, life science now is 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.¹⁶² The number of uninsured and insufficiently insured has risen over the years to reach more than 40 million Americans, and those ranks continue to expand and include more working Americans.¹⁶³ Moreover, accurately gauging the entry of specific scientific capabilities into health care application, especially in the expansive shadow caste by the unpredictability of advances in enabling technologies,¹⁶⁴ is a Herculean task.¹⁶⁵ The present state of some areas of relevant law and scholarship suggest that the law

¹⁵⁹ *See id.*

¹⁶⁰ *See supra* Part I (“Trends in Pharmaceutical R&D”).

¹⁶¹ *See* Michael J. Malinowski, *Biotechnology in the USA: Responsive Regulation in the Life Science Industry*, 2 INT’L J. BIOTECHNOLOGY 16 (2000).

¹⁶² *See generally* Richard D. Lamm, *Universal Health Care Coverage*, 22 J. LEGAL MED. 225 (June 2001).

¹⁶³ There are now approximately 40 million uninsured/insufficiently insured citizens in the United States, and many of those joining the ranks of the uninsured are working Americans. *See* Arthur Jones, *Stretched to the Limit*, NAT’L CATHOLIC REPORTER, Feb. 22, 2002, p. 3, 2002 WL 10828411.

¹⁶⁴ Enabling technologies have had an explosive impact on biotechnology R&D—perhaps mostly to the surprise of the health care community. *See* Malinowski, *Snake Oil*, *supra* note 3, at 23-26.

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.¹⁶⁶

¹⁶⁵ See *supra* note 22 and accompanying text.

¹⁶⁶ Patent law is 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) (the third edition of a technical treatment written by a seasoned European patent attorney). 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. 1092-1099, 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). Ideally, as concern about over patenting in biotechnology became a pressing topic in the early 1990s, law academia would 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, Comment, *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 patenting in biotechnology that caused the market capital of the biotechnology 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," doctrine proven workable for the information technology and publishing sectors, into the body of patent jurisprudence. See, e.g., 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, *PATENTS*, *supra*, at 146 (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 report issued in August 2001, significantly weakening the patent regime would have dire consequences on the behavior of those who invest their careers—whether based in academia or industry—and/or approximately \$500 million dollars and 8-12 years to develop each innovative pharmaceutical, and presumably even more dire consequences for the patients and their families and friends who anxiously await the commercial development and availability of innovative pharmaceuticals. 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 Rae article (proposing a curtailment of patent rights premised on cost savings attributable to use of pharmacogenomics).

One might argue, therefore, that there is a moral imperative in addition to a professional obligation to bridge law and policy with meaningful field work (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 undertake this challenge 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) the delivery of health care, 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.¹⁶⁷ The reforms proposed by this author include revisiting the present state legislative scheme encompassing predictive genetic testing,¹⁶⁸ introducing reliable federal information management systems for both human subject protection and technology transfer,¹⁶⁹ coupling federal oversight capabilities with enforcement such as compliance audits in both human subject protection and technology transfer,¹⁷⁰ and bridging grant compliance and technology transfer within health science institutions.¹⁷¹

¹⁶⁷ See Symposium, *Conflicts of Interest in Clinical Research: Legal and Ethical Issues*, 8 WIDENER L. SYMPOSIUM J. 1-162 (2001); Malinowski, *Snake Oil*, *supra* note 3.

¹⁶⁸ See generally Malinowski, *Snake Oil*, *supra* note 3.

¹⁶⁹ See generally Malinowski, *Institutional Conflicts*, *supra* note 14, at 69-73.

¹⁷⁰ *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 over time through commercialization of pharmacogenomics, to what extent should the law and health care environments be made more welcoming to this technology to accelerate transition into 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, at what price? Consider that by shattering traditional disease classifications,¹⁷² raising the costs of pharmaceuticals,¹⁷³ and introducing a genetic profiling element to drug prescribing and, more generally, to the delivery of care,¹⁷⁴ pharmacogenomics is likely to push the 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,¹⁷⁵ it is time to consider introducing workable yet meaningful safeguards for direct communication between the public and commercial providers of genetic profiling services.¹⁷⁶

The medical, life science, and law communities must work through the entanglement of variables encompassed by these questions to come up with algorithms

¹⁷¹ *Id.*

¹⁷² See Malinowski, *Institutional Conflicts*, *supra* note 14, at n.21; Michael J. Malinowski, *FDA Regulation of Biotechnology*, *supra* note 20, at 224.

¹⁷³ See *id.*

¹⁷⁴ See generally Malinowski, *Snake Oil*, *supra* note 3.

¹⁷⁵ See *supra* note 146 and accompanying text.

¹⁷⁶ Cf. Malinowski, *Snake Oil*, *supra* note 3; Melody Petersen, *TV Ads Spur a Rise in Prescription Drug Sales*, *N.Y. Times*, Mar. 8, 2002, C13.

that work on a collective level, especially since the United States continues to lack reliable federal regulatory oversight of predictive genetic testing services.¹⁷⁷ 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 during the next several years, genetic profiling ultimately should prove as pervasive as genetics in human health.¹⁷⁸ 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 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/law and health policy reforms such as those 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

¹⁷⁷ For thoughtful discussion of the complexities of using genetics in the clinic, *see generally* GENETICS IN THE CLINIC, *supra* note 145.

¹⁷⁸ *See* Malinowski, *Snake Oil*, *supra* note 3, at 33-41 (“The Consequences of Genetic Exceptionalism”).

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 immediate cost savings, and increases in human health and capital. Therefore, the law, medical, and life science communities must rise to the challenge of working through the complexities associated with pharmacogenomics and making the regulatory and other law and policy changes necessary to maximize these human health and economic benefits.