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Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards

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Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards

Michael J. Malinowski
Robin J.R. Blatt*

Many women fear being diagnosed with breast cancer, and rightfully so. Despite the capabilities of modern medicine, the cumulative lifetime risk of getting the disease has risen to one in eight and, despite decades of research, no cures exist. In this Article, the authors explore the commercialization of so-called breast cancer gene tests, based upon genetic alterations linked to the disease. Although the authors fully address this specific technology, they use what constitutes the seminal case of predictive genetic testing to analyze the adequacy of the existing regulatory framework. The authors conclude that the present regulatory system is inadequate and places a dangerous amount of reliance on primary care physicians. Their conclusion is grounded in the observation that most primary care physicians lack sufficient knowledge about this evolving investigative technology—which is highly subject to misinterpretation, and, though potentially helpful to some “high risk” patients, offers questionable clinical value for the general public. The authors set forth numerous proposals to promote both the quality and clinical value of predictive genetic testing so that it conforms to public health standards and can be properly integrated as a reliable component of medical care in specific situations.

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I. INTRODUCTION

OncorMed, Inc. (OncorMed), a small Gaithersburg, Maryland, biotechnology company involved in general cancer testing, announced in January 1996 that it had begun selling a testing service¹ to identify

1. We employ definitions pertaining to genetic testing adopted by the Task Force on Genetic Testing, which was created through the Ethical, Legal, and Social Implications (ELSI) Subprogram of the Human Genome Project (HGP). The ELSI Task Force has defined "predictive genetic test" as the "test of a person's or fetus's genes or gene products for the purpose of determining the presence of abnormalities, including carrier status, that are known to be associated with an increased risk of development of a disease or disorder." Meeting Minutes from the Second Meeting of the Task Force on Genetic Testing 3 (Nov. 14-15, 1995) [hereinafter Meeting Minutes]. As recognized by the ELSI Task Force, the predictive element of this definition must be underscored:

Genetic tests are already an important part of medical practice. In patients with overt manifestations of disease, they can rule out mistaken diagnoses or establish the correct diagnosis promptly, avoiding needless referrals and elaborate workups (e.g. [sic] a test for cystic fibrosis in a child with recurrent pulmonary infections).

ELSI TASK FORCE ON GENETIC TESTING, INTERIM PRINCIPLES 2 (1996). We emphasize the distinction between predictive genetic testing and presymptomatic diagnostic testing. The latter assumes predictability. See *infra* note 12 for further clarification of these terms. We also recognize that breast cancer is not 100% gender-specific, meaning that men too may be stricken with the disease. However, for the sake of simplicity and to reflect the vast majority

the presence of genetic alterations linked to breast and ovarian cancer.² Within a few months, Genetics & IVF Institute (IVF) of Fairfax, Virginia, began to offer a variation of the test³ to any Jewish⁴ woman

of breast cancer patients, throughout this Article we use the female gender to refer to breast cancer patients.

2. The stated purpose of the test is to determine the presence of a specific genetic alteration, or allele, linked to breast and ovarian cancer. The testing process consists of extracting DNA from a blood sample and sequencing the DNA to determine whether the genetic alteration is present. This technology is based upon the discovery that a gene called BRCA1 (breast cancer 1), found on chromosome 17, codes for a protein that has a tumor-suppressor function. See Yoshio Miki et al., *A Strong Candidate for the Breast and Ovarian Susceptibility Gene BRCA1*, 266 *SCIENCE* 66, 66-71 (1994); Stephen C. Rubin et al., *Clinical and Pathological Features of Ovarian Cancer in Women with Germ-Line Mutations of BRCA1*, 335 *NEW ENG. J. MED.* 1413, 1413 (1996) (reporting, however, that this form of inherited cancer is more responsive to clinical treatment); see also Frances S. Collins, *BRCA1—Lots of Mutations, Lots of Dilemmas*, 334 *NEW ENG. J. MED.* 186, 186 (1996) (emphasizing the scientific unreliability of current testing capability). Alterations in the gene may interfere with the production of this protein or with the gene's function in some other way, and thus cause an increased risk of developing breast cancer. Already

more than 130 different mutations have been found in the breast cancer gene.

Some are probably meaningless, and others deadly, but most have not been studied yet. Standard gene tests available today detect only . . . a few of the more common mutations, so a negative test doesn't guarantee that a woman is safe.

Rick Weiss, *Tests' Availability Tangles Ethical and Genetic Codes*, *WASH. POST*, May 26, 1996, at A1; see also D. Shattuck-Eidens et al., *A Collaborative Study of 80 Mutations in the BRCA1 Breast and Ovarian Cancer Susceptibility Gene*, 273 *JAMA* 535, 535-41 (1995) (stating that over 100 distinct mutations of BRCA1 have been identified). A second gene, known as BRCA2, also has been linked to breast and ovarian cancer. See Richard Saltus, *2d Cancer Gene Cited in 1 of 100 Ashkenazi Jewish Women*, *BOSTON GLOBE*, Oct. 2, 1996, at A18 (citing Oct. 2, 1996 issue of *Nature Genetics*). In early 1997, a third gene, CHK, was linked to breast cancer. See Judy Foreman, *Another Gene with Breast Cancer Role Identified*, *BOSTON GLOBE*, Jan. 16, 1997, at A23.

3. IVF uses allele-specific hybridization techniques rather than sequencing.

4. One BRCA1 mutation, 185delAG, is believed to occur in one percent of the people who are of Ashkenazi (Eastern European) Jewish ancestry. See J.P. Struewing et al., *The Carrier Frequency of the BRCA1 185delAG Mutation is Approximately 1 Percent in Ashkenazi Jewish Individuals*, 11 *NATURE GENETICS* 198, 198-200 (1995). Research is ongoing, as other ethnic groups may be more susceptible to inherited breast cancer and, further, inherited susceptibility may be offset by environmental factors not yet identified. Still, according to recent data, one in 50 Ashkenazi women carry at least one of the BRCA1 and BRCA2 mutations that are believed to raise a woman's susceptibility to inherited breast and ovarian cancer. See Saltus, *supra* note 2, at A18. However, only five to ten percent of incidents of breast cancer are believed attributable to inherited genes. See *id.* See generally *The Scientific Questions*, 18 *PERSP. GENETIC COUNSELING* 4 (1996) (estimating that 10% of breast cancers are due to germline mutations); David S. Hilzenrath, *Md. Firm's Gene Test to Intensify Bioethics Debate*, *WASH. POST*, July 25, 1996, at D14 (describing a service to detect predisposition to breast and ovarian cancer). For discussion of the danger of "ethnic genetics," see Ruth Hubbard & Wendy McGoodwin, *The Danger of "Ethnic Genetics,"* *BOSTON GLOBE*, Oct. 13, 1995, at 3. See also E.J. Kessler, *The Secret Shake-Up in the Shiduch, Forward*, *CANCER & US*, July 26, 1996, at 11, 13 (reporting from New York City's Orthodox Jewish Community that, "[d]iagnosed with breast cancer—a terrifying disease

willing to pay \$295.⁵ OncorMed then expanded its service to include tests for genetic alterations of BRCA1 *and* BRCA2 for between \$400 and \$1,200 (the latter for combinations of the genetic alterations).⁶ In the fall of 1996, Myriad Genetic Laboratories, Inc. (Myriad), a Salt Lake City subsidiary of Myriad Genetics, also began selling a combined test for several alterations of the two genes for \$2,400.⁷ All of these companies are actively developing markets for their testing services. According to one report, “[i]n the future, OncorMed is expected to market its testing service to disease management facilities and insurance companies, which would benefit from information about patients’ susceptibility to breast and ovarian cancer, as well as other diseases.”⁸ IVF, Myriad, and OncorMed have not submitted and do not intend to submit their testing services to the Food and Drug

under any circumstances—these women feel they must hide their trouble, traveling far from home for treatment and disguising their hospital stays as out-of-town visits, lest the news of their affliction poison the marriage prospects of their daughters”). It is important to note that OncorMed has directly addressed some of the implications of singling out Ashkenazi Jews for BRCA testing through the formation of a special protocol and information packet to accompany its “Heritage Panel” test, a test for three BRCA mutations found at an elevated level in families of Ashkenazi Jewish descent. See OncorMed Heritage Panel Education and Testing Packet (undated) (on file with authors).

5. See Meredith Wadman, *Women Need Not Apply*, WASH. POST, May 5, 1996, at C3 (reporting that, in collaboration with IVF, Dr. Joseph Schulman is offering the test to Jewish women referred by a physician for \$295); Weiss, *supra* note 2, at A1.

6. See Hilzenrath, *supra* note 4, at D14 (“OncorMed . . . plans next week to introduce a new service that will raise the stakes in one of biotechnology’s biggest ethical debates . . .”); Ridgely Ochs, *New Test Offered for Cancer Gene*, NEWSDAY, July 24, 1996, at A7.

7. See MYRIAD LABORATORIES, INC., BRCA1: GENETIC SUSCEPTIBILITY FOR BREAST AND OVARIAN CANCER 2 (1996); see also Saltus, *supra* note 2, at A18; Sean Taytigan et al., *The Complete BRCA2 Gene and Mutations in Chromosome 13q-Linked Kindreds*, 12 NATURE GENETICS 333, 333-37 (1996) (publishing full sequence of BRCA2 breast cancer gene by Myriad Genetics). To advance compilation of the data needed to raise the clinical value of its BRCA testing, Myriad has established a registry at the Dana-Farber Cancer Institute. See Richard Saltus, *Gene Test for Cancer Risk is Offered*, BOSTON GLOBE, Oct. 25, 1996, at A1.

8. *OncorMed BRCA1 Testing Service Commercialization Enters Second Phase Through New IRB Protocol*, 39 BLUE SHEET 6, 6-7 (1996) [hereinafter *OncorMed BRCA1 Testing Service*]. In contrast, Europe is considering an outright ban on the use of genetic testing information by insurers in the absence of comprehensive self-regulation. See *Insurers Risk Ban Over the Use of Genetic Testing*, DAILY EXPRESS, July 19, 1996, available in Westlaw, 1996 WL 6714032 [hereinafter *Insurers Risk Ban*].

Administration (FDA) for review.⁹ According to their interpretation of existing FDA and other federal regulations, they are not required to.¹⁰

The commercialization of these so-called "breast cancer tests"¹¹ marks the advent of a generation of predictive¹² genetic testing products derived from discoveries reported intensely in the media during the past several years.¹³ The public is demanding more

9. We note, however, that these companies have taken very different approaches to many of the patient issues raised in this Article. We commend the work of OncorMed and, in particular, Dr. Patricia Murphy in developing meaningful protocols for genetic testing. See App. I.

10. See Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4544 (1997) ("The Task Force recognizes that developers of genetic tests who do not rely on federal funds are under no legal obligation to submit protocols to the proposed NGB and have not always obtained IRB approval for validation protocols of tests they plan to market as laboratory services."). However, the FDA has not completely acceded that it lacks the statutory authority to regulate genetic testing. See *OncorMed BRCA1 Testing Service*, *supra* note 8, at 7 ("Currently, the FDA is not regulating the testing; the agency maintains that it has such authority but lacks the resources to review the technology or make and enforce new regulations for the field.").

11. As discussed fully *infra* at note 25, the clinical predictive value of these tests for determining whether an individual who has tested positive for the alleles will suffer breast cancer in her lifetime has not been determined, except for a very small percentage of the population.

12. It is important to distinguish *predictive* genetic testing from reliable *presymptomatic* genetic testing, as the meaning of these terms is being muddled in the current genetic testing debate. The distinction between these terms is certainty, clinically known as "positive predictive value" (PPV), which is defined *infra* at note 25. Presymptomatic genetic testing refers to testing for genetic alterations *causative* of disorders and often controlled by a single genetic alteration, prior to the onset of symptoms. Such disorders include Huntington's Disease and Amyotrophic Lateral Sclerosis (ALS), commonly known as Lou Gehrig's disease. So-called "predictive" genetic testing is also testing for genetic alterations linked to health conditions and disorders. However, due to the influence of other genes and environmental factors over the target health conditions, predictive genetic testing at most offers the general public *estimated* chances of actually developing the health condition.

13. Even years ago, leaders in the field of genetics were responding to "the very real possibility that the explosion of knowledge in the field of genetics will produce a windfall of diagnostic and therapeutic technologies." Philip J. Boyle, *Shaping Priorities in Genetic Medicine*, HASTINGS CENTER REP., May-June 1995, *supp.* at 1; see also Weiss, *supra* note 2, at A1 ("New genetic tests are moving rapidly from research laboratories into doctors' offices, where they are being marketed as a way to predict people's chances of getting common diseases such as colon cancer, breast cancer and Alzheimer's disease."). The truth has become undeniable. "Scores of genetic tests have been developed for dozens of diseases. Some are used to diagnose existing conditions and others are used in healthy people to predict the odds that a disease will occur." *Id.* Representative genetic tests in various stages of development include the following:

Medically useful: (a) APC gene, which is linked to familial adenomatous polyposis condition that leads to colon cancer; (b) MEN gene, which is linked to multiple endocrine neoplasia and indicates a very high risk of cancer of the endocrine glands; and (c) RB gene, which is linked to retinoblastoma--childhood eye cancer;

information about the technology,¹⁴ and other commercial and academic laboratories are introducing their own tests for genetic-influenced disorders that may help assess future disease risk.¹⁵ From a

More research needed: (a) BRCA1 and BRCA2, which have been linked to breast and perhaps ovarian cancer; (b) MSH2 and MLH1, which have been linked to hereditary nonpolyposis colon cancer; and (c) p53, which has been linked to Li-Fraumeni syndrome, an elevated risk of many cancers; and

Little clinical utility at present: (a) p16, which has been linked to malignant melanoma, a serious skin cancer; and (b) APOE-4, which has been linked to Alzheimer's disease.

Id.

14. As recognized by Professor Annas, "The gene has become more than a piece of information; it has become 'a cultural icon, a symbol, almost a magical force.'" George Annas, *Genetic Prophecy and Genetic Privacy*, TRIAL, Jan. 1996, at 19, 24-25 (quoting DOROTHY NELKIN & M. SUSAN LINDEE, *THE DNA MYSTIQUE: THE GENE AS A CULTURAL ICON* 2 (1995)); see also Richard Saltus, *Sounding the Alarm*, BOSTON GLOBE, May 26, 1996, (Magazine), at 14 [hereinafter Saltus, *Sounding the Alarm*] ("No longer merely a scientific schematic, it is now a staple of pop culture. It appears time and again in op-ed pieces, newspaper and magazine articles, and books that tackle the thorny dilemmas of the genetic revolution."). Dr. Richard C. Lewontin, a Harvard scientist who is critical of present priorities in gene research and also affiliated with the Council for Responsible Genetics, a consumer group based in Cambridge, Massachusetts, has coined the term "genomania," that is, "the idea that almost everything—a baby's chin or nose, someone's personality quirks, or a preponderance of men in positions of power—can be explained by genes." *Id.* But see Richard Saltus, *Early Alzheimer's: Do You Want to Know?*, BOSTON GLOBE, July 3, 1995, at 39 [hereinafter Saltus, *Early Alzheimer's*] ("Recently developed gene tests . . . for inherited predispositions to breast cancer and other cancers have raised this issue for an increasing number of families. If any conclusion can be drawn thus far, it's that people are more hesitant and ambivalent about learning their genetic destiny than anyone expected."). It is important to emphasize that industry is attempting to facilitate consumer interest in and demand for genetic testing. For example, "Myriad is currently establishing a genetic testing and information business to identify individuals who have inherited gene mutations which increase their risk for specific illnesses." MYRIAD LABORATORIES, INC., *supra* note 7, at 2. The predominant force that drives consumer demand for a great deal of predictive genetic testing may be social pressure. See Daniel Callahan, *The Genetic Revolution, in BIRTH TO DEATH: SCIENCE AND BIOETHICS* 15 (David C. Thomasma & Thomasine Kushner eds., 1996) ("New medical technologies rarely remain discretionary for long. If they are not legally imposed on people, something hard to do in our western society, they can just as effectively be imposed by social pressure.").

15. See *ASSESSING GENETIC RISKS* (Lori Andrews et al. eds., 1994) (reporting on pervasive, informal genetic testing by research); *ELSI TASK FORCE ON GENETIC TESTING*, *supra* note 1, at 2; Paul H. Silverman, *Commerce and Genetic Diagnostics Laboratories*, HASTINGS CENTER REP., May-June 1995, supp. at S15 ("The prospect of routine genetic diagnostics for a wide variety of diseases ranging from rare monogenetic afflictions (for example, Tay-Sachs) to common polygenic diseases (for example, many cancers) have attracted the attention of commercial testing laboratories and venture capitalists."); Joan Stephenson, *Questions on Genetic Testing Services*, 274 JAMA 1661 (1995) ("As scientists pinpoint genes that underlie such diseases as cystic fibrosis and breast cancer, commercial and academic laboratories are scrambling to provide genetic testing services aimed at diagnosing gene-related disorders and assessing future disease risk."); Ronald Rosenberg, *For Matritech, an Encouraging Prognosis*, BOSTON GLOBE, Feb. 18, 1996, at 80 ("Matritech

business perspective, these laboratories are doing so (1) to generate immediate revenue streams to finance their scientific research and development (R&D); (2) to amass patient data to determine the extent to which their tests predict the onset of breast and ovarian cancer for the general population, thereby giving them the option to sell their tests as kits and charge market prices rather than simply recouping costs;¹⁶ (3) to obtain subject samples for gene sequencing and outpace their science competitors; (4) to accelerate the development of more marketable diagnostics, therapeutics, and maybe even gene therapies; and/or (5) to increase familiarity, acceptability, and demand for such tests among physicians and the public, and thereby perhaps achieve standard care acceptance and insurance coverage for their products.¹⁷

The precedent set by IVF, Myriad, and OncorMed (as well as academic research institutions) conceivably affects all Americans directly. More than five thousand genetic alterations have been identified,¹⁸ and estimates are that every person has four or five genetic alterations linked to serious health conditions.¹⁹ Now that a "critical mass" of the human genome has been mapped through the Human

and other biopharmaceutical firms are developing a new generation of simple diagnostic tools, or exams, to track the progress of the cancer itself in recovering patients.").

16. See *infra* note 64 and accompanying text.

17. According to the ELSI Task Force, the four primary forces fueling expansion of the commercialization and availability of predictive genetic testing are: (1) the reward structure of science, which encourages immediate reporting of findings; (2) public demand for progress in the fight of disease; (3) biotechnology companies' objective of developing markets large enough to make testing profitable; and (4) media coverage of genetic discoveries. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 4. For a general discussion of the inconsistency of insurance coverage in the United States for state of the art medical treatments, see Karen L. Illuzzi Gallinari, Commentary, *The State of the Law on Insurance Coverage for State of the Art Medical Treatments*, MEALEY'S LIT. REP.: BAD FAITH, Oct. 18, 1995, at 16.

18. A catalog of human genes and genetic disorders has been compiled by Dr. Victor A. McKusick, doctor of medical genetics and professor at the National Center for Human Genome Research at John Hopkins University. This catalog, which is updated daily and available on the World Wide Web, lists more than 5,000 genes/genetic disorders. See Ellie McCormack, *Sought-After Counselors Find It's All in the Genes*, BOSTON BUS. J., Apr. 26-May 2, 1996, at 3, 23; see also *Do You Really Want to Know?*, *Nightline* (ABC television broadcast, Apr. 26, 1996) (videotape on file with authors). Consider that, in 1966, this list consisted of just 1,500 entries. *Id.*

19. "According to the British Medical Association, '[g]enetic and part-genetic diseases affect one in every twenty people by the age of 25 and perhaps as many as two in three people during their lifetime.'" Sheila A.M. Mclean, *Genetic Screening of Children: The U.K. Position*, 12 J. CONTEMP. HEALTH L. & POL'Y 113, 114 (1995) (stating also that the proportion of childhood deaths attributable to genetic factors, wholly or partly, is approximately 50%) (citing BRITISH MEDICAL ASSOCIATION, *OUR GENETIC FUTURE: THE SCIENCE AND ETHICS OF GENETIC TECHNOLOGY 1* (1992)).

Genome Project (HGP),²⁰ linkages between genes and health conditions should increase exponentially.²¹ Technology also has made testing for genes associated with health cheaper and easier, and standard medical practice soon will include much more genetic testing.²² Kaiser Permanente, the nation's largest health maintenance organization, already has decided to allow its divisions to offer BRCA genetic testing to its members.²³

The danger is that, absent regulatory safeguards and quality controls, the forthcoming multitude of predictive genetic testing

20. The HGP is a three-billion-dollar initiative launched by the federal government to map the entire human genome by the year 2005. For discussion of the HGP, see generally ROBERT M. COOK-DEEGAN, *THE GENE WARS* 169 (1994); Robert M. Cook-Deegan, *Origins of the Human Genome Project*, 5 RISK: HEALTH, SAFETY & ENV. 100 (1994). The impact of the HGP on the biotechnology industry is addressed in Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. REG. 163, 190-91 (1996).

21. See *Detailed Human Physical Map Published by Whitehead-MIT: STS-Based Map Represents Halfway Point to 100-kb Human Genome Project Goal*, HUMAN GENOME NEWS, Jan.-Mar. 1996, at 5 [hereinafter *Human Physical Map*] ("The new map, which contains more than 15,000 STS DNA markers spaced an average of 199 kb apart, covers almost 95% of the entire genome. . . . Although originally slated for 1988, map completion by Whitehead-MIT and other groups is expected by the end of this year."). The HGP is a "global attempt to identify the blueprint of every individual's genetic makeup." Mclean, *supra* note 19, at 114-15. For a full discussion of the HGP, see Malinowski & O'Rourke, *supra* note 20, at 190-93; Michael J. Malinowski, *Coming into Being: Law, Ethics, and the Practice of Prenatal Genetic Screening*, 45 HASTINGS L.J. 1435, 1441-45 (1994). See also *infra* Part II.A. One of the fundamental goals underlying HGP is "[t]he rapid transfer of technology to industries that can develop economically and medically useful applications . . . that affects us all." ROBIN J.R. BLATT, *CONCEIVING THE FUTURE: THE X'S AND Y'S OF GENETIC TESTING IN PREGNANCY* (forthcoming 1997) (on file with the authors).

22. See Dee Lord, *Something in the Genes*, ABA J., Apr. 1996, at 86; Richard Saltus, *Curbs on Use of Genetic Information Studied*, BOSTON GLOBE, Feb. 23, 1996, at 19. The capability to test for multiple mutations at one time is known as multiplex testing. See Lori B. Andrews, *Prenatal Screening and the Culture of Motherhood*, 47 HASTINGS L.J. 967 (1996) (addressing multiplex testing in the context of prenatal screening). An advanced form of this technology, Multiple Allele Specific Diagnostic Assay (MASDA), developed by Genzyme Genetics in Framingham, Massachusetts, makes it possible to test over 500 patient samples for over 100 known mutations *simultaneously*. See Private Communication between Robin Blatt and Judith King, Former Education and Corporate Communications Manager, Genzyme Genetics (July 1996).

23. According to one report, Kaiser

plans to offer genetic tests to show the predisposition to breast cancer among some of its 6.8 million members. Kaiser guidelines will lay out the process for getting the test, and will probably require any candidates to undergo comprehensive counseling in advance. Patients and their families will be included in a registry and will be followed afterward to monitor the consequences of the test.

Robert B. Whitcomb, *Our Genetically Evolving Future*, PROVIDENCE JOURNAL-BULLETIN, Sept. 5, 1996, at 7B.

services will be overused. Even tests that are good predictors for some people may be overused and misinterpreted by patients, providers, insurance companies, and employers.²⁴ Biotechnology companies can sell their testing services outside major research centers and through the broad community of primary care physicians. This substantiates concern that genetic tests will become widely available to patients without adequate pretest counseling by providers who either “interpret” them without appreciation for the technologies’ predictive limits or, worse, leave patients to make their own interpretations. In other words, genetic testing may be mainstreamed before the predictability of such testing is determined with scientific accuracy. Such tests may become the equivalent of biological tarot cards, subject, like the Tarot, to misinterpretation and overreliance.

This Article explores both the patient-care and public-health implications of commercialization of predictive genetic testing services under the existing regulatory scheme. A central premise is that regulatory safeguards must be introduced to ensure that genetic testing is made available only when it carries scientifically valid predictive value (positive predictive value, or PPV).²⁵ Equally as

24. See Stephenson, *supra* note 15, at 1661 (stating,

[t]he problem with this development, according to a new survey, is that some of the laboratories offering genetic testing are bypassing the admittedly vague regulatory controls or other less formal measures that exist to help assure test validity. Some are also failing to make it clear to physicians and patients that many such procedures are still investigational in nature.

); see also Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4539-44 (1997). This conclusion is supported by a recent study, conducted by Dr. Neil Holtzman, that sampled 594 commercial and 425 nonprofit laboratories (mostly academic institutions) and realized a response rate of approximately 80%. See *id.*; see also Barbara Koenig, *Gene Tests: What You Know Can Hurt You*, N.Y. TIMES, Apr. 6, 1996, at A23 (“Unfortunately, nothing prevents laboratories from offering genetic tests, nor are there any regulations to insure the quality of the tests.”). Although Dr. Holtzman has not yet published the results of his survey, according to one interpretation:

The poll revealed that most commercial enterprises that currently market such tests are doing so without gaining clearance from the Food and Drug Administration (FDA), and thus there is no guarantee that the laboratory tests are performed properly or that they are even appropriate for the disease in question. The researchers also found that many testing organizations are failing to seek approval from institutional review boards—panels composed of physicians, scientists, ethicists, clergy, and representatives from the lay community—which hospitals often establish to discuss whether new procedures or technologies should be put into effect.

The Hazards of Genetic Testing, HARV. WOMEN’S HEALTH WATCH, Dec. 1995, at 6.

25. As explained by the ELSI Task Force, the penetrance of the genetic factor (genotype) is the probability that the related condition will appear in the physical makeup (phenotype) when the genetic factor is present. See ELSI TASK FORCE ON GENETIC TESTING,

important, providers and patients must be educated about both the technology's limitations and their respective legal rights and responsibilities.

Part II presents an overview of genetic testing capabilities, existing regulations, and the dangers of premature use of genetic testing. Part III employs legal storytelling to illustrate implications of the commercialization of genetic testing services. Part IV addresses these implications by presenting diverging theories on the appropriate regulatory response to the advent of commercialized genetic testing services. Part V sets forth proposals for the responsible commercialization of these technologies.

II. TODAY'S TECHNOLOGY, YESTERDAY'S REGULATIONS

Expansive genetic testing capabilities have been a long time in coming.²⁶ Such technology was foreseeable at the commencement of the HGP in 1990.²⁷ Concern about the impact of such testing on

supra note 1, at 9. "The quantitative measurement of penetrance is [] 'positive predictive value (PPV) . . .'" *Id.* The application of PPV to BRCA tests is illustrative of the concept. "The observed lifetime PPV for breast cancer due to inherited BRCA1 mutations is 85%-90% in women in high risk families, but some women with these mutations will develop breast cancer for other reasons." *Id.* at 9-10. To accurately determine the PPV, it must be determined through clinical research what percentage of women with the mutation will get the disease for other reasons. In other words, what percentage of women without the mutation will still get the disease? Further, the percentage of women with the mutation who do not develop the disease must also be determined. Several studies raise some doubts on inherited risk, suggesting that "environmental factors, such as age at first childbirth, diet, and exposure to hormones, can alter the effects of the BRCA1 and BRCA2 genes, and other genes may have an impact as well." Richard Saltus, *New Data Add to Confusion on Breast-Cancer Gene Issue*, BOSTON GLOBE, Apr. 30, 1996, at 9. Due to the factors that must be considered and the potential importance of interaction between factors, "[o]btaining data for PPV may take years to accomplish, particularly for late-onset disorders." ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 10. This BRCA example illustrates that presently the PPV and clinical sensitivity of genetic tests are intrinsically limited. For example, "[m]any different alleles in the same gene (*allelic diversity*) or alleles of different genes (*locus heterogeneity*) can lead to the same disease. . . . Failure of a test to detect all disease-related mutations reduces its clinical sensitivity." *Id.* at 8. A test carries high clinical *sensitivity* when it is immune from being skewed by other substances (such as substances in food or drink) and high clinical *specificity* when it can determine the exact substance(s) linked with a condition. *See id.* at 5-12.

26. Predictions by scientists that genetic technology would greatly improve human health date back at least 15 to 20 years. *See* Saltus, *Sounding the Alarm*, *supra* note 14, at 14.

27. Strong concerns about the uses of genetic information by insurance companies were raised by public officials, such as Congressman Obey, during House appropriations hearings for the HGP back in 1990. *See* COOK-DEEGAN, *supra* note 20, at 169; *see also* DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1991 pt. 4B, at 887-960. In fact, today's pressing genetic

society inspired James Watson, codiscoverer of the double-helix structure of DNA and the first head of the HGP, to insist at the outset of the HGP that a respectable percentage of the annual budget be committed to addressing the project's ethical, legal, and social implications.²⁸

Nevertheless, most public health officials and other regulators, both federal and state, are only *beginning* to become aware of the full implications of new genetic technologies.²⁹ Similarly, the

testing issues were readily foreseeable as early as 1986. See MATTE E. BROM, Note, *Insurers and Genetic Testing: Shopping for that Perfect Pair of Genes*, 40 DRAKE L. REV. 121, 128 (1991) ("In a 1986 survey of biotechnology companies, eight planned to offer genetic tests as a laboratory service for clinicians and researchers, and six predicted that diagnostic kits would be available for sale by 1991.").

28. See COOK-DEEGAN, *supra* note 20, at 237.

29. This is true both domestically and abroad. Domestically, the National Institutes of Health (NIH) and Department of Energy (DOE), through their ELSI program, assembled the Task Force on Genetic Testing and charged it with completing a report by the end of 1997. See generally ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 2. Also, the Clinton Administration recently appointed a fifteen-member National Bioethics Advisory Commission (NBAC) whose initial studies will cover the appropriateness of patenting genes and the rights of patients who participate in genetic research. See Jeffrey L. Fox, *US Bioethics Commission Meets, Outlines Agenda*, 14 NATURE BIOTECHNOLOGY 1533, 1533 (1996) (emphasizing importance placed on genetic privacy issues); Russ Hoyle, *US National Bioethics Commission: Politics as Usual?*, 14 NATURE BIOTECHNOLOGY 927, 927 (1996) ("[A]n effective bioethics commission must take as its mission the review of difficult, or 'big time' research in public before it is done."); Eric Convey, *Mass. Exec. Named to Bioethics Panel*, BOSTON HERALD, July 25, 1996, at 29 (announcing appointment to presidential panel to explore ethical issues surrounding the biotech industry); Charles Craig, *National Commission to Study Ethics of Genetic Medicine*, 7 BIOWORLD TODAY, July 25, 1996, at 1; see also Office of Science and Technology Assessment, National Bioethics Advisory Comm. Proposed Charter, 59 Fed. Reg. 41,584, 41,584-86 (1994) (announcing the establishment of such a commission); *US Agencies Seek Rules on Human Testing*, BOSTON GLOBE, Jan. 23, 1997, at A11 (reporting that five Cabinet departments and two agencies agreed to a formula to share the \$1.1 million operational cost). "In Europe, similar commissions are already well established, from Britain's Nuffield Council on Bioethics (London) and UNESCO's International Bioethics Committee (Paris) to the European Commission's Group of Advisers on Ethical Implications of Biotechnology (Brussels)." Hoyle, *supra*, at 927. Also, in July 1996, the U.K. government announced the establishment of a Human Genetics Commission to serve as a strategic body to monitor medical genetics in response to parliamentary pressure for a unified group with a strategic overview. See *UK Sets Up Human Genetics Commission*, CLINICA, July 1996, at 1 (describing the commission as a nonstatutory body consisting of eminent, independent experts who will report to both health and industry ministers); Michael J. Malinowski, *Globalization of Biotechnology and the Public Health Challenges Accompanying It*, 60 ALB. L. REV. 119, 123-33 (1996). In the United Kingdom, the Medical Research Council is deciding whether it will publicly fund a search for genes that influence IQ-test results. See David King, Editorial, *Business Gets the Upper Hand*; David King Calls for Democratic Decision-Making, GUARDIAN, May 23, 1996, at 19.

genotechnology³⁰ industry has just begun to recognize the need to address ethical concerns regarding the commercialization and responsible applications of its work.³¹ As a result, the regulatory infrastructure necessary for responsible commercialization of genetic technology is being developed *in response to*, rather than in anticipation of, its commercialization. The following is an overview of present genetic testing capabilities, existing regulations, and dangers arising from the premature commercialization of genetic testing.

A. Overview of Genetic Testing Capabilities

Today the scientific community is experiencing a nature movement as forceful as the nurture movement that took force in the 1960s and that set the priorities in science for the decades to follow.³² Behavioral genetics, the nature extreme in genetic medicine, is a burgeoning field grounded in the belief that molecular genetics even

30. Genotechnology is the subset of biotechnology consisting of scientific discoveries associated with human genetics and the HGP. See Malinowski & O'Rourke, *supra* note 20, at 191 & n.165. "Genomics" is another descriptive term, used routinely by industry for this category of technology. See generally BIO '96, INTERNATIONAL BIOTECHNOLOGY MEETING & EXHIBITION, GENOMICS: IMPACT ON HEALTH CARE (1996) [hereinafter BIO '96] (on file with authors) (discussing the impact of genomics on health care).

31. The Biotechnology Industry Organization (BIO) recently formed an ethics committee to deal with privacy and research issues. See Kathleen Day, *Genetics Research Begets Questions; Biotech Industry Seeks Ethics Advice to Deal with Complex Issues*, WASH. POST, May 8, 1996, at A1. This committee

will focus on [the] issue of privacy and on what types of research should and should not be performed, said BIO President Carl Feldbaum. He said executives from American Home Products Corp., Genentech Inc. and Genzyme are heading committees on these and other topics and that the organization is trying to hire a PhD [sic] in philosophy to become its full-time staff member on ethics issues.

Id. Perhaps even more impressive, Novartis, one of the world's largest life-sciences companies (formed through the merger of Ciba-Geigy and Sandoz in December 1996), will voluntarily label its genetically-engineered food products as part of a campaign to educate the public about the advantages of these products—*e.g.*, a significant reduction in the use of pesticides and pesticide residues. See Scott Allen, *Genetically Altered Food to be Labeled*, BOSTON GLOBE, Feb. 25, 1997, at D2.

32. See Saltus, *Sounding the Alarm*, *supra* note 14, at 14 (stating,

If "nurture" was the rallying cry of the 1960s, when changing the social environment through Great Society-style programs seemed the surest way to better lives, the pendulum has swung back in the last 25 years toward "nature" and the belief that genes are decisive components of what and who we are and how we behave.

“points the way to the future of psychiatry.”³³ Recent discoveries linking genes to complex behavior such as depression³⁴ and nurturing³⁵ are reinforcing this belief.³⁶

Generally, when a gene or biological marker linked to a physical or mental condition is discovered, the basic scientific capability to test for the presence of that marker is a given. Thousands of such linkages have been made subsequent to the commencement of the HGP,³⁷ and at a rate accelerating with the passage of time, to the point that linkages are being identified almost on a weekly (if not daily) basis.³⁸ Now that a critical mass of the human genome map has been

33. Erik Parens, *Taking Behavioral Genetics Seriously*, HASTINGS CENTER REP., July-Aug. 1996, at 13 (citing U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, *MENTAL DISORDERS AND GENETICS: BRIDGING THE GAP BETWEEN RESEARCH AND SOCIETY* (1994)) (although emphasizing the danger of straying away from appreciation for environmental factors, recognizing that “much research suggests that genetics may help to explain a partial but significant component of some forms of, for example, schizophrenia, bipolar disorder, and depression”); see also Richard A. Knox, *Study of Mice Links a Gene to Nurturing*, BOSTON GLOBE, July 26, 1996, at A1 (reporting that the objective of scientists working in the field is to identify “molecular handle[s] to try to unravel some of the neuronal circuitry involved in mediating behavior”); Rick Weiss, *Discovery May be Brewing in Search for Genetic Link to Alcoholism*, WASH. POST, July 1, 1996, at A3 (reporting new breakthroughs in discovering genes relating to alcoholism); *Anxiety Linked to Genetics*, N.Y. TIMES NEWS SERVICE, Nov. 29, 1996 (reporting that “[s]cientists have discovered a modest but measurable link between anxiety-related behavior and the gene that controls the brain’s ability to use serotonin”); Parens, *supra*, at 13-18 (“As information about the genetic component of human behavior increases, so, of course, does the number of opportunities for its abuse.”).

34. During the spring of 1996, scientists in Edinburgh, Scotland identified a gene linked to depression that could lead to much more effective treatment. See Nigel Hawkes, *Scientists Identify Gene Linked to Depression; Discovery Prompts Study of Families*, TIMES LONDON, Mar. 15, 1996, available in Westlaw, 1996 WL 6481302.

35. See Knox, *supra* note 33, at A1 (reporting that a team consisting of researchers from Harvard Medical School and Tufts University, through manipulation of a gene called fosB, have created a strain of mice that seem normal in every way except that they ignore their newborn offspring).

36. At the present time, “research suggests that genetics may help to explain a partial but significant component of some forms of, for example, schizophrenia, bipolar disorder, and depression.” Parens, *supra* note 33, at 13.

37. For listings of such discoveries over the past several years, see Malinowski, *supra* note 21, at 1443-44. See also Saltus, *Sounding the Alarm*, *supra* note 14, at 14 (“In recent years, researchers have claimed that homosexuality, schizophrenia, alcoholism, risk taking, violent behavior, and even basic temperamental traits like shyness are governed by genetic variations.”).

38. Recent genetic-linkage discoveries have been made both for the tendency to nurture and the tendency to have strokes. See Peter J. Howe, *Gains Reported Toward Identifying Stroke-Related Genes*, BOSTON GLOBE, July 30, 1996, at A6 (reporting on *Nature Genetics* article and stating that the discovery may create novel opportunities for diagnosis of potential strokes); Knox, *supra* note 33, at A1 (noting a gene, FosB, which is linked to nurturing).

completed,³⁹ the pace of such discoveries is likely to increase exponentially. In fact, although the impact of environmental factors on the function of genes and physical and mental health must not be underestimated, an age governed by molecular medicine, in which a patient's actual and future health can be diagnosed primarily through deciphering genes, is a conceivable possibility.⁴⁰

Biotech companies are using such discoveries to develop and commercialize predictive screening tests for an abundance of health conditions in addition to breast and ovarian cancer. Recent discoveries include genetic links to Alzheimer's,⁴¹ bladder cancer,⁴² cervical

39. See *Human Physical Map*, *supra* note 21, at 5 ("The new map, which contains more than 15,000 STS DNA markers spaced an average of 199 kb apart, covers almost 95% of the entire genome Although originally slated for 1998, map completion by Whitehead-MIT and other groups is expected by the end of this year.")

40. See Annas, *supra* note 14, at 20 ("Molecular medicine, based on deciphering the genes of a patient instead of diagnosing the patient based on signs and symptoms, is said to be just around the corner."); Bio '96, *supra* note 30, at 5 ("[T]he study of genetic variation will enable the identification of patient sub-populations that may respond particularly well or poorly to currently-marketed drugs."); *id.* at 9 ("Drugs developed using genomics technology can be expected to offer advantages in specificity that will result in therapeutics with fewer side effects."); *id.* at 16 ("The ability to eliminate ineffective therapies due to individual therapeutic response will be another way in which genomics will contribute to the reduction in healthcare costs. . . . Genomic diagnosis will provide physicians with a sound basis upon which to prescribe appropriate therapies.")

41. See Eric M. Reiman et al., *Preclinical Evidence of Alzheimer's Disease in Persons Homozygous for the e4 Allele for Apolipoprotein E*, 334 *NEW ENG. J. MED.* 752, 752 (1996) (stating that variants of the apolipoprotein E allele appear to account for most cases of late-onset Alzheimer's disease, and that persons with two copies of one variation appear to have an especially high risk of dementia); Stephenson, *supra* note 15, at 1661-62 ("One such test detects APOE-4 (also frequently denoted as APOE4), a form of the gene that directs the production of cholesterol-carrying protein called apolipoprotein E. Individuals who possess the APOE-4 gene have an elevated risk for developing Alzheimer's disease, particularly those who have two copies of the allele."). Athena Diagnostics, a biotech company located in Worcester, Massachusetts, developed the first specific laboratory test for Alzheimer's disease, a disorder which affects four million Americans. See Richard Saltus, *Worcester Firm Touts First Lab Tests for Alzheimer's*, *BOSTON GLOBE*, Mar. 27, 1996, at 47. According to Athena officials, the company is making the test available as a service under an investigatory protocol, meaning that, like OncorMed and Myriad, Athena will perform the test in-house for samples (blood and cerebrospinal fluid, obtained by a spinal tap) submitted by providers for a fee of \$195. See *id.*; see also Jerry E. Bishop, *Test Improves Detection of Alzheimer's*, *WALL ST. J.*, July 12, 1996, at B3 (discussing genetic test that may improve the accuracy of diagnosing Alzheimer's disease). The clinical utility of the test, as defined by Athena, is that it may be used to distinguish Alzheimer's from other forms of dementia, some of which can be treated. See *id.*; see also Saltus, *Early Alzheimer's*, *supra* note 14, at 39 ("With the discovery last week of a gene that causes an aggressive inherited form of Alzheimer's disease, it will soon be possible to offer a test to people in at-risk families, where, on average, half the children of any affected parent will get the gene."); Saltus, *supra*, at 47.

42. See Rosenberg, *supra* note 15, at 80. In comparison with the traditional bladder test now on the market, this test (1) is performed on a simple urine sample, thereby avoiding

cancer,⁴³ colon cancer,⁴⁴ obesity,⁴⁵ prostate cancer,⁴⁶ and tumor growth associated with a spectrum of common cancers.⁴⁷ Researchers are even developing an “Ides of March” genetic test to serve as a crude indicator of a person’s life span.⁴⁸ By conservative estimates, “some 50,000 gene markers will be developed as a result of molecular biology and translated in not easy-to-employ biochemical assays, genetic tests, new drugs, and genetic therapies.”⁴⁹

Unfortunately, the discovery of genetic alterations linked to many health conditions comes well before those discoveries can be turned into therapeutics and reliable predictors of disease in specific

the painful cystoscopy—the insertion of a fiber-optic rod through the urethra and into the bladder—which is required for the current test; (2) costs \$50 rather than \$300; and (3) is much more accurate and, therefore, can detect the earliest signs of cancer. *See id.*

43. Matritech, a biotech company located in Worcester, Massachusetts, is working on a test for cervical cancer that would be an improvement to the Pap smear procedure. *See Tina Cassidy, Matritech Says It Will Begin Trials on a More Accurate Colon Cancer Test, BOSTON GLOBE, Apr. 20, 1996, at 25.*

44. Trials are being conducted on a colon cancer test that allegedly is more than twice as sensitive (70% compared to 33%) as the current leading diagnostic test for early-stage colorectal cancer. *See Cassidy, supra* note 43, at 25.

45. A gene-signaling system has been discovered through the independent work of two biotech companies, Amgen and Millennium Pharmaceuticals. Amgen discovered a gene that makes leptin, an enzyme linked to obesity in rats; Millennium has identified a genetic receptor for leptin. *See Richard Saltus, Piece of Obesity Puzzle Found in Cambridge: Drug Researchers Locate Key Receptor, BOSTON GLOBE, Dec. 29, 1995, at 1.* The work of these companies has pushed their competitors, and “researchers have now found five genes involved in regulating food intake and weight.” *Id.*

46. At least one biotech company is working on an improved test for prostate cancer. *See Cassidy, supra* note 43, at 25.

47. Through research in an extended family with a high incidence of kidney cancer, scientists have discovered a gene known as FHIT. *See Richard Saltus, Gene Eyed in Many Cancers, BOSTON GLOBE, Feb. 25, 1996, at 9.* This gene is believed to make a protein that helps to keep the body’s cells dividing in an orderly, regulated way. Control over cell growth is lost when the gene is damaged by environmental pollutants, diet, or other factors. *See id.* The FHIT gene may prove to be an invaluable lead for understanding how normal cells become malignant in a variety of common cancers, including those of the esophagus, stomach, and colon; and possibly including ovarian, cervical, lung, and bone cancers. *See id.*; *see also Cancer Research Yields ‘Time Bomb’ for Tumors, BOSTON GLOBE, Apr. 24, 1996, at 8* (“Cancer researchers have engineered what they call the first genetic time bomb, set to go off inside tumor cells when they blow their cover by producing telltale proteins.”).

48. Research involving APOE variations indicates linkages to general susceptibility to diseases of aging. *See Jerry E. Bishop, A Gene Gives a Hint of How Long a Person Might Hope to Live, WALL ST. J., Oct. 19, 1995, at A1* (“If some scientists are correct, the test may be the forerunner of what could be called the Ides of March tests, a panel of blood tests that might predict, as the onlooker foretold for Julius Caesar, when one might die—but not how.”). The researchers responsible for this discovery admit that APOE is, for any one individual, a “sloppy indicator.” *Id.* Nevertheless, there is the possibility that such a test could be used by insurers who engage in grouping. *See infra* note 113 and accompanying text.

49. Boyle, *supra* note 13, *supp.* at S2.

individuals.⁵⁰ Although the availability of therapeutics to offset genetic predispositions will make genetic testing much less controversial, that time is years away for most conditions.⁵¹ Similarly, for families other than those with high occurrence of disease *and* well-documented pedigrees, determining predictability is a laborious, subject-intensive process that may take more than a decade to complete.⁵²

50. See Mclean, *supra* note 19, at 116. As recognized by the U.K. House of Commons Science and Technology Committee, “[w]hile a knowledge of how the gene works, when established, should, in time, lead to new drug development, through rational drug design, at present it can take 15 years to develop and gain approval for a new pharmaceutical product.” *Id.* (citing 1 SCIENCE AND TECHNOLOGY COMMITTEE, HOUSE OF COMMONS, HUMAN GENETICS: THE SCIENCE AND ITS CONSEQUENCES xxxvi (1995)); see also Boyle, *supra* note 13, *supp.* at S2 (

People will be tested for conditions that might never fully express themselves as a disease, or only express themselves in a mild form. For example, nearly 20 percent of persons who carry the gene for fragile-X, the most common form of inherited mental retardation (affecting one in every 2,500 live births), will never express any form of mental retardation. Yet if parents knew their children’s genetic status, they might treat unaffected children as if they were mentally disabled.

); Saltus, *Sounding the Alarm*, *supra* note 14, at 14 (“But today, 15 or 20 years after the first predictions that gene technology would greatly improve health, scientists have been far more successful in finding defective genes than in fixing or replacing them.”); *infra* Part II.C. Examples of the practical effect of this gap between the discovery of a genetic linkage to a health condition and treatment derived from that discovery are plentiful:

Genetic researchers, in their quest to understand a terrifying disease, have once again delivered the means to predict a person’s future, but not yet to alter it.

With the discovery last week of a gene that causes an aggressive inherited form of Alzheimer’s disease, it will soon be possible to offer a test to people in at-risk families, where, on average, half the children of any affected parent will get the gene.

....

Recently developed gene tests for Huntington’s disease and for inherited predispositions to breast cancer and other cancers have raised this issue for an increasing number of families. . . .

The test for familial, early-onset Alzheimer’s might be relevant for 500,000 or more Americans who are at risk for having the gene

Unlike the more common type of Alzheimer’s disease, which affects an estimated 4 million people in the United States and generally appears in the late 60s, the 70s or 80s, the early-onset form can show up even among people in their 30s.

Saltus, *Early Alzheimer’s*, *supra* note 14, at 39.

51. See Malinowski & O’Rourke, *supra* note 20, at 174-77 (discussing status of gene therapy). Dr. Ruth Hubbard and Jonathan Beckwith recognize that, even for conditions such as Huntington’s and multiple sclerosis, which are known to be caused by a single genetic variation that is responsible for the failure of the cell to make a single protein, science has not been successful in turning genetic discoveries into treatments. Multifactorial conditions multiply this complexity. See Saltus, *Sounding the Alarm*, *supra* note 14, at 14.

52. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1; *infra* Part II.C.

Nevertheless, a deluge of fully commercialized genetic testing services and kits is well within sight.⁵³ Even by conservative estimates,⁵⁴ expectations are that the DNA testing market (1) for neoplastic (tissue growth) diseases will reach \$340 million in 1998; (2) for infectious diseases will exceed \$300 million by 1998; and (3) for genetic diseases will exceed \$65 million by 1998.⁵⁵ This market could experience a several-fold increase with the availability of probes for polygenic (multifactorial) diseases.⁵⁶ To build these markets, the developers and manufacturers of genetic tests need patient data both (1) to establish clinical predictability, and (2) to sequence and better understand the most fundamental intricacies of specific genes. The latter will enhance the predictive capabilities of resulting tests and perhaps lead to other products, including therapeutics and even gene therapies. The commercial possibilities, including patient-care possibilities, create a powerful incentive to make research-stage genetic tests available to the public.

Many developers and manufacturers of genetic tests now are making investigatory, predictive genetic testing available to the public.

53. The commercial interests developing genetic technologies are nearly as diverse and plentiful as the underlying discoveries:

Major diagnostic companies (Abbott, Boehringer Mannheim, Miles, Baxter, Beckman, Becton Dickenson, Ciba-Geigy, Johnson & Johnson, Eastman Kodak, Bio Rad, etc.) are developing a variety of technologies by inhouse invention and through alliances and acquisitions. . . .

In addition to the established major commercial players, hundreds of start-up companies have been formed to exploit various niche diagnostic capabilities generated in academic research laboratories.

Silverman, *supra* note 15, *supp.* at S15; *see id.* *supp.* at S17 ("Regardless of the numerous unknowns in the development of DNA diagnostics, the potential demand for these services will continue to grow. Attractive financial rewards assure that DNA diagnostics will become a significant commercial enterprise.").

54. These estimates, generated during the Spring/Summer of 1995, are conservative because they predate (1) the precedent for commercialization of genetic testing services without FDA oversight now being set by OncorMed and Myriad, (2) the advancement of pending FDA reforms to streamline the FDA review process for biotechnology products, (3) growth in consumer demand for genetic tests due to both increased media coverage and marketing efforts on the part of biotechnology companies, and (4) a globalization of biotechnology and expansion of worldwide markets. *See* Malinowski, *supra* note 29, at 123-33.

55. *See* Silverman, *supra* note 15, *supp.* at S16; *see also* BLATT, *supra* note 21 (noting that the revenues presently being generated are from biogenetic analysis for prenatal testing of chromosome conditions). *But see* Vicki Glaser, *Myriad Pulls IPO from Inhospitable Market*, 15 NATURE BIOTECHNOLOGY 14 (1997) (reporting that Myriad pulled its follow-on public offering, and speculating that lack of investor interest may have been attributable to below lower-than-anticipated sales figures for its BRCA1 and BRCA2 tests).

56. *See* Silverman, *supra* note 15, *supp.* at S16.

Although IVF, Myriad, and OncorMed are commercializing their tests, other companies and research laboratories are making research-stage genetic tests available in a more discreet manner. In 1994, the Committee on Assessing Genetic Risks assembled by the Institutes of Medicine documented pervasive informal genetic testing by research laboratories,⁵⁷ and the ELSI Task Force on Genetic Testing has reached similar conclusions regarding both research and commercial laboratories that report results to patients.⁵⁸

The emergence of predictive genetic tests with implications for broad segments of the population, such as the APOE-4 (Alzheimer's) test, is raising concern among public health officials and providers

57. See generally ASSESSING GENETIC RISKS, *supra* note 15.

58. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 2-4; see also Richard Saltus, *Survey of Labs New Tests Concerns Genetics Specialists*, BOSTON GLOBE, Oct. 28, 1995, at 14 ("Commercial and academic labs are moving so quickly to offer gene tests predicting future health risks that some are bypassing regulatory and ethical quality controls, specialists in genetics say."). According to a survey conducted by Dr. Neil Holtzman's office at John Hopkins University:

Although any lab performing clinical genetic tests must register with HCFA under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) [42 C.F.R. § 493.1 (1996)], the study found that about 10% of responding labs failed to do so. Several labs (8%) did not use external review (including proficiency testing) to help assure quality. Many labs intended to market genetic tests to non-geneticist providers, even though most respondents were of the opinion that such providers knew little about these tests. Responding labs also tended to view the current regulatory scheme as inappropriate.

Dr. Stephen Hilgartner described the highlights of his follow-up interviews of selected respondents to Holtzman's survey. He found a variety of commercial genetic testing activity, ranging from large companies seeking to offer comprehensive test services to smaller firms developing specific tests for particular market niches.

Meeting Minutes, *supra* note 1, at 1-2. Other studies, including a study undertaken by the Genetic Screening Study Group in the spring of 1992, have reached similar conclusions about the pervasiveness of genetic discrimination. See, e.g., Carol I. Barash & Joseph S. Alper, *A Study on Genetic Discrimination*, 8 GENETIC RESOURCE 43, 43 (1994) ("The study found that a wide variety of social institutions engage in genetic discrimination. People reported discriminatory practices by insurance companies (life, health, disability, and mortgage), in employment (hiring and promotion), by the military, schools and universities, adoption agencies, and health care providers."); Lisa N. Geller et al., *Individual, Family, and Societal Dimensions of Genetic Discrimination: A Case Study Analysis*, 2 SCIENCE & ENGINEERING ETHICS 71, 75 (1996) (concluding that, of the 917 questionnaire respondents, 455 indicated instances of genetic information discrimination). For anecdotes of genetic information discrimination, see generally *id.*

In contrast with the United States's incremental approach to protection against genetic discrimination by insurers, see, e.g., Health Care Portability and Accountability Act, Pub. L. No. 104-191, 110 Stat. 1936 (1996), European countries are considering an outright ban on the use of genetic testing information by insurance in the absence of comprehensive self-regulation. See *Insurers Risk Ban*, *supra* note 8.

who understand the limitations of this technology and are sensitive to its potential impact on the lives of patients and their families.⁵⁹ However, with such understanding comes appreciation for the difficulty of introducing a satisfactory regulatory response to the multitude of genetic technologies approaching and entering commerce.⁶⁰

B. Existing Regulations

Predictive genetic testing services, performed in-house by the tests' developers and manufacturers, are square pegs in the rubric of federal regulation. The FDA regulates the production of reagents, probes, or test kits manufactured for use by others in laboratories and, therefore, genetic tests manufactured and sold for others to perform.⁶¹

59. See Stephenson, *supra* note 15, at 1661-62 ("Concerns about genetic testing have escalated with the recent emergence of tests that may have implications for large segments of the population.").

60. See Boyle, *supra* note 13, *supp.* at S2 ("Genetic technologies are by no means a homogenous lot; they have varied medical and social effects, and are intended for diverse populations with distinct severity of illnesses, both actual and potential.").

61. Such tests constitute "diagnostic kits" subject to regulation under the Medical Device Amendments of 1976 (MDA), 21 U.S.C. § 360k(a) (1994), and the FDA has exercised some considerable discretion in the area of home testing. See, e.g., Daniel J. Murphy, *FDA Ridiculed for Blocking At-Home Drug Testing*, INVESTORS BUS. DAILY, Oct. 1, 1994, at A4 (reporting FDA's prohibition of the sale of drug-testing kits to parents). Pursuant to the MDA, the FDA regulates medical devices in the context of a classification scheme that distinguishes among devices based upon the concerns they raise about safety and effectiveness. The FDA is required to classify each medical device intended for human use into Class I, II, or III. See 21 U.S.C. § 360(C)(a)(1). Class I devices pose no unreasonable health risk (general controls that ensure, among other things, safe labeling and that the produce is safe when used as directed), while Class II devices carry special controls, such as performance standards necessary to ensure safety and effectiveness. See *id.* Class III devices are those represented to be life-sustaining or life-supporting and those presenting potentially unreasonable risk of illness or injury, and they require premarket approval to assure safety and effectiveness. The premarket-approval process requires submission of a premarket-approval application (PMA), which the FDA must review before it authorizes marketing. However, there is an exception for diagnostics that are the substantial equivalent of others already approved. See *id.* § 360k. Still, additional review is required for *any* change in a device's design. See 21 C.F.R. § 807.81(a)(3)(i) (1996). There also are regulations for device construction and manufacture, known as good manufacturing practice (GMP) requirements, that establish detailed requirements for all stages of the manufacturing process. To monitor compliance, the MDA require factory inspections at least once every two years for Class III products and post-marketing reporting. See 21 U.S.C. § 360(h); 21 C.F.R. § 803.1-.58.

Because of their complexity, when genetics-based diagnostics are subjected to review, they generally are labeled Class III devices. See Malinowski & O'Rourke, *supra* note 20, at 206. Before developers make these products available to the public, they must apply for an Investigational Device Exemption (IDE), which is analogous to the Investigational New Drug Application (IND) required for new drugs. See *id.* Device manufacturers can

However, manufacturers and private laboratories may avoid the routine FDA review process for diagnostics and comply with applicable federal regulations by manufacturing and using their own reagents in-house and selling testing *services* through primary care physicians.⁶² Such reagents are called “home brews” because they are manufactured and used within the same facility, and a number of such tests are being developed and made available to the public.⁶³

Home brews may be marketed as established products or, to limit product liability where clinical efficacy is not yet established, labeled investigatory.⁶⁴ Although the developers of investigatory tests are

circumvent the IDE requirement by establishing that there is an independent means by which to confirm the validity of their test.

This may be accomplished (1) through the 510(k) clearance process, by establishing that the product is the substantial equivalence of a previously marketed product or (2) by obtaining premarket approval (PMA), which requires a full documentation of safety and effectiveness and an advisory committee review. However, the general absence of approved genetic diagnostics on the market makes these exceptions unlikely for predictive genetic tests. In fact, the manufacturers of such kits should expect added requirements, such as a requirement that counseling accompany test results. The FDA imposed such a requirement when approving a home AIDS test in May of 1996. *See Weiss, supra* note 2, at A1.

62. *See Medical Devices, Classification/Reclassification; Restricted Devices; Analyte Specific Reagents*, 61 Fed. Reg. 10,484 (1996) (to be codified at 21 C.F.R. pts. 809 & 864) (proposed Mar. 14, 1996) (“FDA currently regulates the safety and effectiveness of diagnostic tests that are traditionally manufactured and commercially marketed as finished products. However, in-house developed tests have not been actively regulated by the Agency and the ingredients used in them generally are not produced under FDA assured manufacturing quality control.”); *see also OncorMed BRCA1 Testing Service, supra* note 8, at 7 (reporting on the FDA statement that it has the authority to regulate but not the needed resources and expertise to actually do so).

63. *See FDA Needs to Regulate Genetic “Home Brews,”* 14 NATURE BIOTECHNOLOGY 1627 (1996) [hereinafter *FDA Needs to Regulate*]; Stephenson, *supra* note 15, at 1662. The ELSI Task Force, in its investigation of genetic testing practices, found that “at least some companies appear to be circumventing this process by offering genetic testing services themselves—using the very probes and other products that would be subject to FDA regulation if these products were sold to others as part of a kit for the purpose of genetic testing.” Stephenson, *supra* note 15, at 1662. The distinction is that, if a developer performs an assay in its own laboratory, that laboratory may be designated a *reference* laboratory, and uncertainty regarding how reliably a third party will perform the test is removed. *See id.*; *see also* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 12 (“Often [laboratories developing new tests] use home brews as well as reagents purchased ‘for research use only’ in clinical tests, although neither have been approved for clinical use.”). Still, as discussed in Part II.C., the *results* of predictive genetic tests are prone to misinterpretation by both providers and patients and, therefore, may be misused clinically.

64. As discussed above, a BRCA test is being marketed without self-restraint by IVF, while OncorMed is limiting its potential liability by restricting access to its testing service. *See Weiss, supra* note 2, at A1. There are two main labeling options for products without established clinical efficacy:

For research use only and not for use in diagnostic procedures. The manufacturers of such tests are not permitted to make claims regarding the test

allowed to charge consumers only enough to recapture costs, commercialization of these tests enables them to generate a revenue stream, gather needed patient data, and build standard-care acceptance of their technologies. Standard-care acceptance means enhanced acceptability among physicians and the public, limits on product liability, and perhaps insurance coverage.⁶⁵ Also, the costs of investigatory tests may be considerable, depending upon the stated research objective.⁶⁶

Private laboratories performing genetic testing services also are essentially immune to federal laboratory-quality assurances imposed by the Health Care Finance Administration (HCFA) through the Clinical Laboratory Improvement Amendments (CLIA).⁶⁷ Under

beyond statements that identify and explain its research purpose, and such tests are not supposed to be used clinically (the results are not supposed to be reported to subjects); and

For investigational use only. Informed consent must be obtained before the test is performed, and those tested must be apprised of the facts that performance characteristics are not yet established and data is being collected (the test is being offered) for that purpose.

See id.; *see also* BLATT, *supra* note 21. However, off-label uses of tests, where a test approved by the FDA for one purpose is used for another, are commonplace. *See* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 11 (“The Task Force opposes off label use of genetic tests without independent validation and is exploring new policies to deal with this problem.”). A prime example of widespread, off-label testing is the use of the maternal serum alpha-fetoprotein (MSAFP) screening for the presence of Down’s syndrome. Although the test was initially designed to screen for the presence of neural tube disorders in the unborn, researchers and labs noticed a correlation between low MSAFP results and Down’s syndrome, thereby creating a new application for its use. *See* BLATT, *supra* note 21. The shortcomings of this labeling system include the following: (1) despite these requirements, it is not uncommon for laboratories to offer testing labeled “for research purposes only” to patients and report the results to them; (2) off-label uses are common; (3) the FDA, although aware of compliance problems in laboratory genetic medicine, lacks the resources to bring laboratories into compliance and is hesitant about removing products from the marketplace out of fear of causing disruption and arousing public and political opposition; (4) compounding this problem, the FDA is presently in a state of flux and there is a moratorium on new regulations; and (5) although laboratories are required to be aware of the regulatory status of the products they use and are expected to use them appropriately, consumers and medical practitioners are frequently unaware of the regulatory status of the laboratory tests being performed. *See id.*

65. *See The First BRCA1 Test Hits the Market; Are Oncologists, Patients Ready?*, CANCER LETTER, Jan. 26, 1996, at 1, 1-5 [hereinafter *First BRCA1 Test Hits the Market*].

66. For example, if the stated objective of providing a genetic testing service is gene sequencing, the cost may increase tenfold. *See id.* at 2.

67. *See* 42 C.F.R. § 493.1 (1996); Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4545 (Nat’l Insts. Health 1997) (“Many tests currently on the market have not been systematically validated nor subject to external review. . . . The Task Force is concerned about the lack of Federal law or regulation covering genetic tests . . .”). As enacted, CLIA prescribed general regulations for medical laboratories, but it applied only to (1) laboratories involved in testing specimens originating

CLIA, a laboratory must demonstrate *analytical* validity of its tests and their components, but there is no *clinical* validity requirement.⁶⁸ In other words, the CLIA validity requirement is satisfied when a genetic test to determine the presence of a specific genetic alteration does so accurately, even though the test may offer no clinical predictability.⁶⁹ There is no required express showing that the alteration tested for has any bearing on the subject's health. The only CLIA patient-care safeguard on clinical quality is the requirement that the proposed clinical protocol receive institutional review board (IRB) approval when an investigatory test enters the human-trial phase.⁷⁰ Academic laboratories are required to report to their standing IRBs, but "[t]he situation with respect to IRBs is murkier for biotechnology companies and commercial laboratories. They also may consult an IRB of an academic institution with whom they have ties, or they may form their own IRB—a practice that has the potential for a conflict of interest."⁷¹

out-of-state and (2) laboratories processing specimens from individuals on Medicare and Medicaid. CLIA 88 set forth revised regulations that more uniformly govern laboratory testing involving human samples by establishing general laboratory standards for personnel, proficiency testing, quality control, and quality assurance. *See generally* Summary of United States Product Liability Law (May 24, 1996) (research memorandum prepared by Kirkpatrick & Lockhart LLP, Boston, MA) (on file with authors).

68. *See* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 14-15.

69. The ELSI Task Force's Subcommittee on Laboratory Quality's "main theme [is] that genetic testing is unique and better assurance of its quality is needed." Meeting Minutes, *supra* note 1, at 5; *see also id.* at 6-7, 8 (stating that even the "high complexity" category under CLIA does not adequately address the unique nature of genetic tests). The failure of CLIA to address the impact of genetic tests on patient care is addressed in Boyle, *supra* note 13, *supp.* at S7 ("[T]he FDA's standards would consider a test to screen infants for a genetic anomaly 'effective' if it yields an accurate diagnosis, even if no treatment exists Accepting such narrow judgments of effectiveness may . . . create substantial harm by providing information that can cause anxiety, stigmatize, and promote invidious discrimination.").

70. *See* Stephenson, *supra* note 15, at 1662. An organization planning clinical validation studies is supposed to file its protocol with a properly constituted IRB competent to review clinical validation protocols. *See* Joseph Palca, *Institutional Review Boards: A Net Too Thin*, HASTINGS CENTER REP., May-June 1996, at 4. This requirement reflects the original purpose of IRBs, to protect the autonomy of human subjects participating in research. *See id.* For discussion of the increased dependence on IRBs to resolve genetics issues due to proposed disbandment of the Recombinant DNA Advisory Committee (RAC), *see infra* note 257 and accompanying text.

71. Stephenson, *supra* note 15, at 1662; *see infra* notes 245-247 and accompanying text (proposing national IRB standards); Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. at 4544 ("The Task Force is concerned that the high workload of IRBs, their variability in community representation, in evaluating protocols, and in expertise germane to the review of genetic tests, as well as the conflicts of interest that can arise in local review, impairs current review of genetic tests that warrant stringent scrutiny."). *See generally* JOHN ABRAHAM, SCIENCE, POLITICS AND THE PHARMACEUTICAL INDUSTRY: CONTROVERSY AND BIAS IN DRUG REGULATION (1995)

The general lack of regulatory quality control on genetic tests, which raises questions about their fundamental reliability,⁷² is exacerbated by the fact that very few specific guidelines for these tests have been formally developed and introduced by the medical profession.⁷³ “[L]ack of consensus about what type of screening should be offered means that there is also no clear guidance for state policy makers adopting mandatory screening plans” even on issues such as the testing of fetuses for BRCA1 and BRCA2 variations.⁷⁴ Also, reliance on state regulation to monitor (in the ongoing manner necessitated by the research nature of the technology) the quality of genetic testing services is misplaced for, there too, “the field of laboratory licensure and monitoring remains in a state of flux.”⁷⁵

(exploring the capture theory in the context of IRBs, and suggesting that those from the medical profession who serve on IRBs reap tremendous financial rewards and, due to revolving-door staffing of IRBs, may even receive R&D funding from the manufacturer whose products they are reviewing); ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 11 (“The Task Force recognizes that IRBs differ widely in their approach to clinical protocols and in their policies regarding what constitutes research in their purview.”); Advisory Committee on Human Radiation Experiments, *Research Ethics and the Medical Profession*, 276 JAMA 403, 403-09 (1996) (calling for alterations in the IRB component of the federal system to protect human subjects).

72. See Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 61 Fed. Reg. 10,484 (1996) (to be codified at 21 C.F.R. pts. 809 & 864) (proposed Mar. 14, 1996); *FDA Needs to Regulate*, *supra* note 63, at 1627 (

As a result, neither patients nor practitioners have assurance that all ingredients in the laboratory developed tests are of high quality and capable of producing consistent results.

[The] FDA is concerned that the present situation with respect to in-house developed tests, in which these ingredients are essentially unregulated and therefore of unpredictable quality, may create a risk to the public health.

); see also *The Hazards of Genetic Testing*, *supra* note 24, at 6 (reporting on Dr. Holtzman’s survey).

73. But see *infra* notes 245-246 and accompanying text (addressing how professional opposition to BRCA testing outside research centers is resulting in initiatives to develop such guidelines).

74. Andrews, *supra* note 22, at 991.

75. BLATT, *supra* note 21(

While almost every state public health department has a laboratory licensing bureau that is supposed to monitor the quality of laboratory services, many do not have standards designed specifically for genetic laboratory studies (*i.e.*, DNA analysis) and performance requirements are not always enforced. Some laboratories have gone for years without an on-site visit.

). An exception is the State of New York, which has some meaningful laboratory quality authority that is enforceable and has regulatory language addressing the use of investigational genetic testing. See Meeting Minutes, *supra* note 1, at 7 (

New York cannot impose “cease and desist” orders on labs failing to meet *voluntary* PT [proficiency testing] standards, and for this reason the state does not recognize the voluntary lab standards promulgated by the College of American

Perhaps most importantly, circumvention of the FDA review process also may avoid the FDA's tight control on advertising.⁷⁶ Advertising carte blanche is a troubling proposition in the context of providers dealing directly with biotechnology companies and

Pathologists [CAP]. However, New York is empowered to revoke a lab's license for ignoring the recommendations of lab surveyors.

); *see also* Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. at 4545 (discussing how New York requires certification of all laboratories performing clinical genetic tests on state residents).

76. According to some accounts, FDA officials have all the power and discretion of tax collectors—discretion enhanced by the ambiguity of the regulations they enforce. *See, e.g.,* James G. Dickinson, *Will Anybody Sue FDA?*, MED. MARKETING & MEDIA, Oct. 1993, at 100, 102 (“The Food, Drug and Cosmetic Act’s failure to address pharmaceutical marketing activities that are neither ‘advertisements’ nor ‘labeling’ created the gray zone in which both industry and FDA take liberties. Congress simply failed to foresee the innovations that modern communication technologies [advertising] could spawn.”). As explained by Dr. Dickinson:

Advertising alone is defined as “commercial speech” and is thus subject to less First Amendment protection than labeling or non-commercial speech. But FDA has been able to tie advertising’s statutory dependence on the content of approved labeling to a broad array of “labeling” materials in such a way that companies “have no freedom of speech rights when it comes to advertising prescription drugs, compared to the way in which those rights are commonly understood and interpreted by the courts for other industries.”

Id. (quoting Richard T. Kaplar, Vice President of the Washington-based Media Institute). Dr. Dickinson alleges that, “[b]ecause FDA has excessive coercive power in its ability to approve an advertiser’s products for market, and Congress has shown no interest in balancing FDA’s First Amendment incursions, the regulation of drug advertising and promotion should be handed over to the Federal Trade Commission.” *Id.* at 103-04. Dr. Dickinson, citing other authority, contends that the FDA’s definition of “deception” is “the basis for the mischief created by the FDA’s regulation of advertising” because the FDA declares ads or promotional materials “deceptive” unless they contain a “fair balance.” *Id.* at 104 (quoting Kaplar). In practice, according to Dr. Dickinson, “any message promoting some pharmaceutical must also present virtually all negative information about the product.” *Id.* (quoting Kaplar). Citing a book by Paul H. Rubin, an Emory University economics professor, Dickinson sets forth the following proposals for reform:

FDA should (1) cancel all recent initiatives restricting promotion of off-label uses; (2) allow manufacturers to advertise any reasonable claim for which reliable scientific evidence exists; (3) abolish the “brief summary” requirement for consumer advertising; and (4) allow unrestricted advertising of drugs, subject only to regulation for “falsity” but not for “deception” as currently defined.

Id. Nevertheless, the hyping of health-care product features by their manufacturers is a pervasive problem:

So endemic is the practice of hyping product features the facts clearly don’t support that FDA deputy commissioner Mary K. Pendergast, speaking in October 1994 before the House Subcommittee on Regulation, Business Opportunities, and Technology, was moved to uncharacteristically straightforward language. “Promotion of unapproved uses by company sales representatives,” she stated, “is a major problem.”

Greg Critser, *Oh, How Happy We Will Be*, HARPER’S MAG., June 1996, at 39, 47.

institutional laboratories to run extraordinarily novel tests on patient samples. These are tests that, without predictability defined through scientifically reliable clinical data, are highly subject to misinterpretation. The dependence of both providers and their patients on the developers of genetic tests for information—information test developers are compiling on an *ongoing* basis from patient data—could not be greater. Ironically, because test developers are the entities with the most information about their evolving technology, advertising restrictions that are too intrusive could exacerbate rather than lessen misinterpretation by cutting providers and their patients off from the most up-to-date data.⁷⁷

The FDA, in response to the actions taken by IVF, Myriad, and OncorMed, has proposed regulations to bring genetic testing services (and home brews in general) more directly within its purview.⁷⁸ Specifically, the FDA would like to regulate the active ingredients used in genetic tests. The FDA's proposal is to classify "active ingredients," chemicals or antibodies that are useful only in testing for one specific disease or condition, as analyte specific reagents (ASRs), which are subject to controls.⁷⁹ This labeling would require suppliers

77. Historically, advertising of health products accompanied the spread of journalism during the Civil War and was targeted to reach consumers. See ABRAHAM, *supra* note 71, at 42. However, this was followed very quickly by dependence by doctors on the "pharmacopoeias" for knowledge about specific drugs and their measured doses. Soon, drug manufacturers began to make standard preparations available, and

a close relationship based on mutual interest evolved between the big pharmaceutical companies in the U.S. and American physicians; the latter could extend their professional power since only they had the knowledge to prescribe the new science-based drugs, while the large high technology firms create a unique prescription market, in which they had a clear advantage over other medicine makers.

Id. In an age of burgeoning medical science, of a deluge of genetics products, and of competition to attract and retain patients under managed care (by, among other things, offering them the latest treatments), providers' need for information could not be greater. Where products are being made available under investigatory protocols, their developers and manufacturers may be the only entities with such information.

78. See Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 61 Fed. Reg. 10,484 (1996) (to be codified at 21 C.F.R. pts. 809 & 864) (proposed Mar. 14, 1996). *But see* Weiss, *supra* note 2, at A1 ("The Food and Drug Administration, already on the defensive amid corporate claims of over-regulation, has declared it has the authority to regulate genetic tests but hastens to add that it has no plans to do so."); ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 15 ("The Task Force has requested a legal opinion from FDA as to whether, if it has the authority to regulate the development of genetic test services, it can limit the duration of the investigational stage.").

79. Although ASRs generally are subjected to general Class I controls, those determined to carry a high risk may be designated for Class III controls, which include a premarket approval requirement, or they may be regulated by the Center for Biologics

of such active ingredients to register with the FDA and provide lists of the ASRs they are supplying to laboratories for use in developing tests. These suppliers then would be held to good manufacturing standards, which require FDA reporting of all adverse events possibly attributable to products.⁸⁰ The FDA also has left open the possibility of directly regulating in-house genetic testing services at a later date.⁸¹

Ironically, however, the advent of commercialization of genetic testing by OncorMed and Myriad is juxtaposed against weighty political and public pressures on the FDA to streamline, expedite, and privatize its review process.⁸² Despite recent self-reforms,⁸³ this

Evaluation and Research (CBER) because their use presents particularly high risks. *See* Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 61 Fed. Reg. at 10,484-86.

80. *See id.*; 21 C.F.R §§ 803.1-.58, 820.1-.198 (1996).

81. In the Proposed Rules, the FDA states:

However, at a future date, the agency may reevaluate whether additional controls . . . may be especially relevant as testing for the presence of genes associated with cancer or dementing diseases becomes more widely available. Additional controls might include a broad array of approaches, ranging from full premarket review by FDA to use of third parties to evaluate analytical or clinical performance of the tests.

Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 61 Fed. Reg. at 10,486.

82. *See* John Schwartz, *FDA Often Blamed for Problems that Aren't Agency's Fault*, WASH. POST., July 15, 1996, at A17 (reporting how the pharmaceutical industry's trade organization brought 140 disease victims to Washington to lobby for reform); *cf.* Matthew Rees, *What Makes David Kessler Run?*, WKLY STANDARD, June 3, 1996, at 25 (stating that, rather than a political victim, "the Commissioner of the [FDA] is an amazingly resourceful political animal"). The most dramatic features of the proposed FDA reform legislation are privatization of the review process (using private companies to help review clinical data) and a six-month (180-day) time limit on the review of all drugs by 1998—a dramatic reduction compared to the average of 12 months. *See* The Food and Drug Administration and Accountability Act of 1995, S. 1477, 104th Cong. (1995) (bill introduced by Sen. Nancy Kassebaum); Malinowski & O'Rourke, *supra* note 20, at 210-23; Robert Pear, *Lawyers and Lobbyists Help Guide Effort by Republicans to Speed Drug Approvals*, N.Y. TIMES, Mar. 4, 1996, at A15 ("Republicans on the Senate Committee on Labor and Human Resources and the House Commerce Committee, joined by some Democrats, have concluded that Congress must revise the F.D.A. laws to give patients swifter access to new drugs and devices."); Ronald Rosenberg, *Biotech Group Hits Kennedy's FDA Stance*, BOSTON GLOBE, Apr. 26, 1996, at 90 ("Citing scientific advances over the past 50 years, the biotech industry wants to abolish the two-track approval process for biology-based drugs. That process now requires separate approvals for a biological drug, its manufacturing process and for every lot or batch produced."); *see also* Jeffrey L. Fox, "Nitty-Gritty" FDA Guidelines Wanted Sooner Not Later, 14 NATURE BIOTECHNOLOGY 698, 698 (1996) (stating that reforms are expected by late summer which will lessen the burdens on biologics manufacturing). Other proposed reforms include: (1) mandatory review of all "breakthrough" drugs for killer or untreatable diseases in four months, two months faster than today; (2) a requirement that the FDA farm out its work to private companies if it does not meet the proposed review deadlines by 1998; and (3) the opportunity for companies to

pressure has been mounting, especially for cancer and AIDS—diseases that affect millions of people and, not coincidentally, major research and development (R&D) areas for biotechnology companies.⁸⁴

petition for automatic approval for sale in the United States of any therapy that is approved in certain foreign countries if the FDA misses its deadline (the FDA then would have 30 days to block the sale, by declaring the treatment unsafe or unproven). See Luran Neergaard, *FDA Resists Claiming Potential for Dangerous Errors*, BOSTON GLOBE, Feb. 22, 1996, at 3. The public pressures on the FDA also have been profound. See, e.g., Editorial, *The FDA and Shannon McDermott*, BOSTON GLOBE, Apr. 15, 1996, at 10 (“Janet McDermott[, who was brought to Washington by pharmaceutical trade groups,] is waging a valiant struggle to get medication that will prevent the seizures suffered by her daughter Shannon. But Shannon’s plight should not encourage support for a bill in Congress that would force the [FDA] to speed up the approval process for new drugs.”). These forces have joined, for drug companies have learned the power of teaming up with patients. See Pear, *supra* (“Drug companies contribute substantial sums of money to patient-advocacy groups, but those groups insist that they are not unduly influenced by the money.”). The FDA reform movement is the culmination of a general trend to deregulate the commercialization of pharmaceuticals. See Critser, *supra* note 76, at 40 (“Today, the American patient is inexorably being transformed into his own pharmacist. The trend is most apparent in the pages of magazines, with their weirdly text-heavy ads. Less obvious are the marketing fests taking place in the nation’s doctors’ offices and emergency rooms.”).

83. See BILL CLINTON & AL GORE, REINVENTING DRUG AND MEDICAL DEVICE REGULATIONS 4-5 (1995) (executive branch/FDA proposals for self-reform); KENNETH B. LEE, JR. & G. STEVEN BURRILL, BIOTECH 97: ALIGNMENT, THE ELEVENTH INDUSTRY ANNUAL REPORT 34-36 (1996); *For Biotech Firms, FDA Rules Have Much to Please*, BOSTON GLOBE, Nov. 23, 1996, at 90 (“[B]iotechnology executives are breathing a lot easier these days about such big up-front investments now that the [FDA] has revamped a host of regulations governing the industry.”). These proposed reforms, many of which now are in the process of allegedly being implemented, were referred to by some in the industry as “the most significant and sweeping in 50 years.” CLINTON & GORE, *supra*, at 4-5. The reforms included proposals to (1) eliminate requirements that each company seek a separate license for each facility where it plans to manufacture a drug, (2) eliminate the requirement that each batch of a biotech-developed drug be sent to the FDA to test, and (3) impose a 30-day deadline for the FDA to respond to a company that has submitted additional information requested after the FDA has put a clinical trial on hold. See *id.* Many of these proposals have been incorporated into Senator Kassebaum’s FDA reform bill. See *supra* note 82 and accompanying text; see also Pear, *supra* note 82, at A15 (reporting that industry experts helped write an FDA bill regarding speeding up approval for new drugs).

84. See generally Elizabeth C. Price, *Teaching the Elephant to Dance: Privatizing the FDA Review Process*, 51 FOOD & DRUG L.J. 651 (1996); *Cancer Diagnostics*, MED. TECH. STOCK LETTER (Piedmont Venture Group, Berkeley, CA), Apr. 18, 1996. “Within days after the Republicans won control of Congress in 1994, some gay rights groups saw an opportunity to win speedier access to new, unapproved treatments for AIDS by rewriting Federal drug laws.” Pear, *supra* note 82, at A15 (discussing new FDA regulations regarding new drug approval process); see also Tanya E. Karwaki, Note & Comment, *The FDA and the Biotechnology Industry: A Symbiotic Relationship?*, 71 WASH. L. REV. 821, 821-22, 834-37 (1996) (addressing reform). This strategy appears to be working, for in response to the political and public pressure, the FDA already has expedited approval of drugs that fight AIDS and cancer. See Pear, *supra* note 82, at A15; Laurie McGinley, *FDA to Quickly Clear Merck AIDS Drug, after Approving Abbott’s Treatment*, WALL ST. J., Mar. 4, 1996, at B3 (“On Friday . . . the [FDA] approved Norvir, known generically as ritonavir. That approval came just 72 days after Abbott filed its application—the fastest drug approval in the

Moreover, the manufacturers of medical devices and diagnostics are pressuring the FDA by organizing and calling for reforms favorable to their products.⁸⁵ The drive to reform the FDA does, however, have its

agency's modern history. And it came just one day after the advisory panel backed its approval." It is important to note, however, that many consumer advocacy groups oppose the "premature" commercialization of genetic testing:

The National Breast Cancer Coalition, for example, a patients' rights group, opposes open marketing of a test for the so-called breast cancer gene, BRCA1. At the risk of sounding as paternalistic as the doctors they often fight against, members said the test's general ambiguous results may trigger unnecessary panic in many women while reassuring others who should remain vigilant.

Weiss, *supra* note 2, at A1.

85. According to the General Accounting Office (Congress's investigator), the average time required for the approval of new drugs has fallen in the last decade from 33 to 19 months. However, acceleration of FDA review of drugs has not been matched for diagnostics. See 142 CONG. REC. S3203 (daily ed. Mar. 29, 1996) (statement of Sen. Edward Kennedy acknowledging that the review process is slower for medical devices and various animal vaccines); Neergaard, *supra* note 82, at 3 ("Today, the FDA spends six months reviewing breakthrough drugs and 16 months reviewing nonessential medicines. Medical devices take much longer."); Pear, *supra* note 82, at A15 ("The agency has accelerated the process of reviewing AIDS drugs, but patients with other life-threatening conditions contend that those drugs receive preferential treatment," and the FDA has not had similar success in accelerating approval of devices and food additives.). See, e.g., *FDA Delays Approval of New Test for Diabetics*, BOSTON GLOBE, Feb. 27, 1996, at 12 ("Diabetics pleaded with the government yesterday to approve the first pain-free way to measure blood sugar, but a panel of specialists said there was no proof the machine works well enough to keep their disease at bay."); *id.* ("I can't tell you how frustrating it is to know this device exists but is just out of reach of Bonnie," said Glenn Sklar of Columbia, Md., who draws blood from his 3-year-old's finger six times a day."). Some argue that the FDA's approval of Olestra, a fat substitute, reflects organization of the Grocery Manufacturers of America, see Pear, *supra* note 82, at A15, and that the FDA's recent approval of Interneuron's antiobesity drug, the first obesity drug approval in over 20 years, reflects the FDA's responsiveness to biotechnology. See Ronald Rosenberg, *Antiobesity Drug Cleared by FDA; Available Soon*, BOSTON GLOBE, Apr. 30, 1996, at 3 (reporting that Redux, developed by Interneuron Pharmaceuticals Inc., was the first new obesity drug approved in 22 years). To create a counterpart to BIO and the Pharmaceutical Research and Manufacturers of America (PHARMA) and a voice for device manufacturers in the FDA reform movement, the device manufacturers are organizing. Specifically,

{a}fter years of being lumped with the biotechnology industry, Massachusetts' medical device companies yesterday announced the formation of their own trade association. Known as the Massachusetts Medical Device Industry Council, or MassMEDIC, the group intends to have a voice in pending reforms at the Food and Drug Administration and in local business and government issues that affect the industry.

Ronald Rosenberg, *Medical Device Firms Form Trade Association*, BOSTON GLOBE, May 7, 1996, at 43 (defining the industry as 200 member companies that employ more than 15,000 people in Massachusetts, create more than three percent of all manufacturing jobs, and generate collective revenues of \$3.5 billion). The formation of MassMEDIC coincides with enhanced FDA responsiveness to the manufacturers' industry. According to former Commissioner Kessler, the FDA has shortened the time it takes to review a device from 134 days in 1994 to 90 days. See *id.* Presently, the FDA is modifying rules that govern export

opponents, most notably former Commissioner David Kessler⁸⁶ and Senator Edward Kennedy.⁸⁷

licenses for medical device products that have not been approved by the agency, that govern pilot testing private-industry review of some low-risk medical devices, and modification of safety and inspection procedures for devices. *See id.*; *see also* Kate C. Beardsley, *Medical Devices-Regulation and Reform*, in *ALI-ABA COURSE OF STUDY MATERIALS: BIOTECH '95 BUSINESS, LAW, AND REGULATION*, Nov. 2-3, 1995, at 255; *FDA Lays Out Plan to Reduce Delays, Costs in Approval Procedures*, *BOSTON GLOBE*, Apr. 4, 1996, at 6 (reporting that FDA has launched a pilot test to determine if outside groups could assume some of the reviews of routine medical devices now handled by FDA scientists for low and moderate risk devices like electronic thermometers and surgical gloves). More specifically, the manufacturers' industry supports proposals that include: (1) exempting (by moving from Class II to Class I) an additional 125 medical device categories from premarket notification requirements, thereby exempting a total of 570 categories (about one-third) from this requirement; (2) allowing the export of devices without an IND exemption; and (3) adopting "an approach similar to that used in the European Community in which device firms have their device applications reviewed by a third-party scientific organization accredited by the government." *Id.*; *see also* Malinowski, *supra* note 29, at 134-42. Under this approach, "a manufacturer pays a third-party organization for its review, the third-party organization notifies the government of the results, the device is marketed without government review, and the government monitors the device after it is on the market for subsequent safety problems." Beardsley, *supra*, at 280. FDA responsiveness to the device manufacturers' industry has, however, accompanied new reporting requirements:

The FDA has issued final regulations specifying new requirements for reporting serious problems with medical devices, as required under the Safe Medical Devices Act of 1990. . . . It will also provide the necessary assurance of product safety to enable the FDA to clear innovative devices for marketing more quickly.

....

Under the new requirements, medical facilities must report all serious device-related injuries or illnesses within 10 days. . . .

Manufacturers have been given 5 days to report to the FDA any device-related incident that requires immediate action to protect the public health. The time limit for the rest of the manufacturers' reports to FDA on device-related deaths and serious injuries or illness is 30 days. This gives manufacturers time to investigate incidents and provide the FDA with detailed information on adverse events.

Stuart L. Nightingale, *From the Food and Drug Administration*, 275 *JAMA* 585, 585 (1996).

86. According to former Commissioner Kessler, the proposed reforms could endanger the health of Americans. *See* Neergaard, *supra* note 82, at 3; *Legislation Puts Public Health at Risk, FDA Chief Tells Panel*, *BOSTON GLOBE*, May 2, 1996, at 9. For a detailed discussion of former Commissioner Kessler's position on this issue, *see* Malinowski, *supra* note 29.

87. *See* 142 *CONG. REC.* S3203 (daily ed. Mar. 29, 1996) (statement of Sen. Edward Kennedy regarding the FDA Reform Markup); Rosenberg, *supra* note 82, at 90. In the words of Senator Kennedy:

Most recently, we reduced the delays in approving prescription drugs with user fees. As a result, we are now approving drugs faster than the United Kingdom. We have fixed the drug lag. In fact, the United States approves more important new drugs faster than any other country in the world.

....

The FDA review process significantly impacts the economy of the United States, for “[t]he products regulated by the F.D.A. account for 25 percent of the nation’s economic output.”⁸⁸ Nevertheless, the biotechnology aspect of the FDA reform movement is grounded in more than the profit motives of biotech companies. With the exception of predictive genetic testing services, biotechnology products have been more highly regulated than traditional pharmaceuticals.⁸⁹ Biotech drugs and therapeutics generally are classified as biologics and, as such, are subject to requirements imposed by both the Federal Food, Drug, and Cosmetic Act (FDCA)⁹⁰ and the Public Health and Services Act (PHSA).⁹¹ Because of fundamental differences in the regulatory approaches taken under these statutes, an entire dimension of added regulation is imposed upon biologics. Specifically, “[t]he primary objective of the FDCA is to ensure the safety and effectiveness of the final product, with controlling the manufacturing process a secondary concern. In contrast, biologics regulation under the PHSA is focused on ‘rigid control of the manufacturing process’”⁹² The practical effect on biologics has been that, to reach the market, developers and manufacturers have had to negotiate an entanglement of licensing and other requirements that front-load their financial investment.⁹³ Self-

. . . The [proposed] legislation says you have to examine all of them, all of the drugs within the 6 months. . . .

So now instead of bringing focus and attention of the gifted and able scientists out at FDA on those drugs that could be breakthrough drugs in cancer, in AIDS, in hepatitis, in all kinds of diseases, we are going to divert their attention to looking after the “me-too” drugs that can make extra bucks for the pharmaceutical companies.

142 CONG.REC. S3203-04 (daily ed. Mar. 29, 1996).

88. Pear, *supra* note 82, at A15.

89. See JAMES T. O’REILLY, FOOD AND DRUG ADMINISTRATION §§ 13-15 (2d ed. 1993) (detailing drug regulation, specifically the approval process, safety and quality issues, and economic and labeling issues); Gary E. Gammerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 213 (1994) (arguing that, in retrospect, the divergent regulatory emphasis of the Biologics Act and the FDCA were appropriate when biologics were crude mixtures or biological extracts); Malinowski & O’Rourke, *supra* note 20, at 205.

90. 21 U.S.C. § 360k(a) (1994).

91. 42 U.S.C. § 262.

92. Malinowski & O’Rourke, *supra* note 20, at 205-06 (quoting Gammerman, *supra* note 89, at 213); see also Gammerman, *supra* note 89, at 220-26 (analyzing the utility of the Biologics Act).

93. See Gammerman, *supra* note 89, at 230-33; Malinowski & O’Rourke, *supra* note 20, at 205-13, 215-24. Establishment licensure requirements have mandated that products used in Phase III trials produced in the intended commercial-scale manufacturing facility and that only the company that manufactures the biologic may obtain and hold the

reforms by the FDA to eliminate some of the most unduly burdensome licensing and other requirements imposed upon biologics have come too late to quell the organization of the biotechnology industry and frustrated consumers awaiting products. International competition stemming from the establishment of the European Medicines Evaluation Agency (EMA) should inspire more self-reform by the FDA and perhaps produce a new commitment to international collaboration in drug review and approval.⁹⁴

The impact of regulatory uncertainty on the biotech industry has provided an incentive to “Coase around”⁹⁵ and reform the existing FDA review process.⁹⁶ Moreover, the reform movement is fueled by genuine concern that, “[i]n this increasingly complex scientific world, where the half-life of knowledge is growing shorter and shorter every day, it’s going to be impossible for the F.D.A. to maintain in-house the full range of expertise and experience that will be needed.”⁹⁷ Despite

marketing licenses. Accordingly, in comparison with traditional drug developers, CBER has forced biotech developers to commit more financial resources to manufacturing before they know if they have an approvable product. See Gammerman, *supra* note 89, at 230-31.

94. See generally John Ashworth, *Development of the European Biotechnology Industry*, 33 CAL. W.L. REV. 83 (1996); Malinowski, *supra* note 29.

95. See Ronald H. Coase, *The Problem of Social Cost*, in *THE FIRM, THE MARKET AND THE LAW* 95, 99 (1988) (arguing that parties will be driven to overcome market interferences, whether caused by regulations or contractual provisions, to reach maximum efficiencies).

96. FDA actions have had, and continue to have, a profound impact on the market appeal of biotechnology. See Malinowski & O'Rourke, *supra* note 20, at 215-24. This is true even for relatively “mature” biotech companies with diverse technology, such as Genzyme Corp., an established biotechnology company located in Cambridge, Massachusetts. See Steve Bailey & Steven Syre, *After the Fall*, BOSTON GLOBE, Mar. 28, 1996, at 41 (reporting that vote by FDA advisory committee recommending approval for limited uses of Septrafilm, a membrane product designed to prevent the adhesion of organs and tissue after some operations, caused a two-day fall in Genzyme stock).

97. Pear, *supra* note 82, at A15 (quoting Sen. Bill Frist, who is a heart surgeon). A prime example of the innovative products at issue is Olestra, a fat-based substitute for conventional fats manufactured by Procter & Gamble. See Nightingale, *supra* note 85, at 585. In a flourish of controversy, the FDA approved this drug but imposed enhanced post-marketing obligations. See Henry Blackburn, *Sounding Board: Olestra and the FDA*, 334 NEW ENG. J. MED. 984, 984 (1996) (“Procter & Gamble will be required to conduct studies that monitor consumption and examine Olestra’s long-term effects. The FDA’s Food Advisory Committee will review these studies in a public meeting within 30 months.”). This decision may be an indication that the FDA is beginning to recognize that truly innovative products may require more than the FDA’s limited resources:

Clearly, the FDA is becoming more aware of the need for epidemiologic studies and clinical trials with adequate statistical power to detect effects and monitor human safety. The agency apparently also has the fortitude to stick to its guns, as it has done, for example, in the cigarette controversy by maintaining that nicotine is an addictive drug. But the FDA does not have the statutory authority, the staff, or the funding to examine adequately the benefit and safety of food

the short "half-life" of its underlying science, the work necessary to fully assess clinical applications takes years. These problems are exacerbated by the FDA's resistance to accept scientific evaluations of technology by the rest of the industrialized first world, a resistance presumably due to a belief in the superiority of United States science and scientific capability.⁹⁸ The success of the HGP, the globalization of the science community responsible for the biotechnology revolution, and the realization of meaningful global telecommunications support the introduction of uniform, international scientific standards for compiling and evaluating clinical data.⁹⁹

The strength of the FDA reform movement reduces, but does not make impossible,¹⁰⁰ the likelihood that a comprehensive regulatory response to the commercialization of genetic testing services will be introduced in the immediate future. Without such FDA reform, other biotechnology companies will follow the precedent set by IVF, Myriad, and OncorMed. Dangers arising from the widespread availability of investigatory, predictive genetic testing services must,

additives generated by the powerful food industry and its sophisticated technology. Moreover, there are now serious political pressures on the FDA, including informal proposals that it become a rubber-stamp certifying body for industry. There are even threats to abolish the agency. In this climate, it is understandable, if unfortunate, that the FDA has to set priorities and choose carefully where to do battle.

Id. at 986.

98. In the words of Senator Barbara Mikulski, a Maryland Democrat, "If we can use NATO weapons, why can't we use drugs from NATO countries?" Neergaard, *supra* note 82, at 3. Despite former Commissioner Kessler's assertions to the contrary, gaps in approval between the United States and Europe do exist and, at times, are extreme. For example, although the FDA only recently approved dexfenfluramine, "in Europe, where it has been used for 10 years, an estimated 10 million patients have been treated with no epidemiological signal indicating any behavioral problem in clinical usage." Ronald Rosenberg, "Take a Pill," *Lose Some Weight*, BOSTON GLOBE, Apr. 15, 1996, at 91 (noting that three fat-fighting drugs are entering the United States market: dexfenfluramine by Interneuron Pharmaceuticals, Inc., known as Redux; sibutramine, with the trade name Meridia, by Knoll Pharmaceutical, Inc., a unit of BASF Corp; and orlistat, with the trade name Xenical, by Hoffmann-La Roche, Inc.).

99. See generally Malinowski, *supra* note 29. See also Malinowski & O'Rourke, *supra* note 20, at 218 (noting that the FDA standards should be harmonized with international medical standards).

100. A personal observation is that the ongoing work of the ELSI Task Force and consumer groups such as the National Breast Cancer Coalition and the Jewish Women's Coalition on Breast Cancer could make this issue a priority on Congress's agenda. See Richard Saltus, *Jewish Women's Group Warns of Risks of Cancer-Gene Testing*, BOSTON GLOBE, Jan. 17, 1997, at B2 (reporting on formation of a coalition that includes the Combined Jewish Philanthropies, National Council of Jewish Women, Beth Israel Deaconess Medical Center, and Jewish Community Centers of Greater Boston to challenge testing for inherited breast cancer genes).

therefore, be identified, thoughtfully considered, and addressed without further delay.

C. *Dangers Arising from the Premature Use of Genetic Testing*

Predictive genetic testing services are, in the aggregate, biological tarot cards subject to misinterpretation by both patients and their physicians.¹⁰¹ The predictive capability of many genetic tests remains scientifically undefined for the general population.¹⁰² This type of testing must be conclusively distinguished from presymptomatic genetic testing. The latter constitutes a reliable and meaningful predictor only for a small number of conditions—conditions usually caused by a single genetic mutation.¹⁰³ Only these few conditions, such as Huntington's and Tay Sachs disease, can be diagnosed conclusively through genetic testing.¹⁰⁴ Even when such conditions

101. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 14 (reporting that a test is ready for routine use only when it has been carefully assessed for (1) sensitivity, (2) positive PPV, and (3) clinical utility). The ELSI Task Force has identified the following aspects of genetic testing as bases for special consideration by public health officials and other policy makers:

predictability seldom approaches certainty; often no independent test is available to confirm the prediction of a genetic test (only appearance confirms the prediction); no interventions are yet available; those tested may be subject to psychological distress, discrimination, and stigmatization; ethnicity may influence genetic makeup; [and] most health providers have received little training in genetics.

Id. at 3; see also Weiss, *supra* note 2, at A1 ("Genetic tests differ from many medical tests because they often provide very vague answers, such as, 'You have a gene that gives you a 70 percent chance of getting breast cancer in the next 20 years.'").

102. See *supra* note 25 and accompanying text.

103. See *supra* note 25; see also ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 8 ("In only a small proportion of patients with common disorders, such as breast cancer or malignant melanoma, do inherited mutations at a single gene locus contribute significantly to the occurrence of the disease."). Examples of the clinical limitations of modern genetic science are almost as plentiful as the genetic linkage discoveries that so captivate the media and the public. Consider the APOE-4 discovery:

Two-thirds of people who develop Alzheimer's later in life have ApoE4. Having just one copy confers three times the average risk of developing the disease; having two copies raises the risk to beyond 90% (The risk of developing Alzheimer's disease is 2% at age 65, but about 10% at age 85.) However, many people with Alzheimer's do not carry even one copy of ApoE4, and some who have two copies of ApoE4 do not develop the disease.

The Hazards of Genetic Testing, *supra* note 24, at 6; see Bishop, *supra* note 48, at A1 (describing blood tests identifying the gene Apoe, which will eventually help determine how long a person lives).

104. See Stephenson, *supra* note 15, at 1661 (

The Task Force investigators discovered that while academic laboratories were more likely than the biotechnology companies to offer tests for single gene

can be diagnosed through genetic testing, the rate of expression may vary; with many genetic conditions, severity remains an open question.¹⁰⁵ Most often there is no available treatment,¹⁰⁶ or treatment exists but is price-prohibitive.¹⁰⁷ In addition, in the absence of uniform federal regulatory oversight, the quality of laboratory performance is questionable.¹⁰⁸

disorders, such as cystic fibrosis, fragile X syndrome, and muscular dystrophy, the latter are far likelier to be engaged in developing or offering tests for complex genetic disorders, such as Alzheimer's disease, breast cancer, and hereditary nonpolyposis colon cancer, and in conducting population testing for such disorders.

105. See, e.g., COOK-DEEGAN, *supra* note 20, at 242 (discussing clinical heterogeneity in the context of cystic fibrosis).

106. In the absence of therapeutics and gene therapies, most predictive genetic tests offer few options:

For example, the only options now available to a woman who learns that she is predisposed to breast cancer are prophylactic mastectomy (in hopes that cancer would not develop in the residual amount of breast tissue) or frequent clinical breast exams and mammograms. Physicians have little to offer in terms of preventive strategies to patients who discover that they have a markedly increased risk of developing Alzheimer's disease by virtue of having two copies of the APOE-4 allele.

Stephenson, *supra* note 15, at 1662; see Hilzenrath, *supra* note 4, at D14 ("Should the patient have her breasts or ovaries removed as purely preventive measures, when there is no guarantee that the surgery would prevent the disease, and no assurance that cancer would develop in the absence of the surgery?"); Richard Saltus, *Genetic Clairvoyance*, BOSTON GLOBE, Jan. 8, 1995, (Magazine), at 14 ("One of the lessons patients and counselors have learned from this experience is that knowing one's genetic fate is not for everyone—especially when, as is the case with Huntington's, knowing what's ahead doesn't help one to avoid it.").

107. A prime example is the treatment for Gaucher Disease. See *Gaucher Disease: Current Issues in Diagnosis and Treatment*, 275 JAMA 548, 548 (1996) (

Despite the success of enzyme therapy, treatment is limited by the cost of the agent.

[This] makes it imperative to determine the lowest effective initial and maintenance dosages and the most cost-effective dosage for clinical response, to define the appropriate clinical indications for treatment, and to establish uniform methods to optimize outcome assessment.

108. See Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4545-46 (1997) (expressing concern over the absence of federal law and regulation to ensure the laboratory quality of genetic tests). Due to the novelty of widespread commercialization of predictive genetic testing services, those scrutinizing them tend to rely heavily on anecdotal evidence. According to one account:

Citing case studies reported to the Task Force, Dr. Holtzman pointed out other problems: 1) laboratory error in performing and interpreting genetic tests; 2) ordering of genetic tests for inappropriate reasons; 3) restriction by managed

More troubling, due to the absence of adequate clinical data, health care providers cannot interpret the results of predictive genetic tests for most of their patients with any reliability *even when they are knowledgeable about genetics*.¹⁰⁹ This interpretation problem is exacerbated because the current generation of health care providers does not possess such knowledge.¹¹⁰ Their lack of genetics education

care organizations of the labs in which tests on their subscribers can be performed; and 4) maintaining confidentiality of genetic test results.

Meeting Minutes, *supra* note 1, at 2.

109. See Stephenson, *supra* note 15, at 1661 (“Interpreting the results of such tests is difficult, in part because the rate of false negatives is unknown.”); Brom, *supra* note 27, at 126. Fully assessing the PPV of existing genetic testing capability for individual patients could take a decade or more. Moreover, it may be that, in the aggregate, environmental factors control approximately 50% of physical characteristics, and that each of us carries multiple genetic predispositions for disease. See *id.*; cf. ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1.

110. See *The First BCAl Test Hits the Market*, *supra* note 65, at 2 (“Available data suggest that many primary care providers lack the knowledge about genetics that’s necessary to educate their patients and ensure informed consent for genetic testing” (quoting Caryn Lerman, associate professor of medicine and psychiatry at the Georgetown University Lombardi Cancer Center)); Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. at 4546 (“A provider’s need for knowledge is particularly keen when tests are in transition from research to clinical use and when clinical utility is still under investigation and there are no established practice guidelines.”); see also William C. Felch & Donald M. Scanlon, *Bridging the Gap Between Research and Practice*, 277 JAMA 155 (1997) (arguing that the research and provider communities must work together to bring medical technology into patient care). At the meeting of the National Task Force on Genetic Testing held in April 1996, representatives of the biotechnology industry placed the responsibility of informed consumption of genetic testing services on physicians. In response, “Doctors said they were still getting up to speed in genetics and would be unable to stem the tide of patient demand if testing were not subject to regulatory restrictions.” Weiss, *supra* note 2, at A15; see also ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 24 (

Several studies have documented the deficiencies in health care providers’ level of knowledge about genetics and genetic tests. As opposed to the results of a serum sodium or a complete blood count, which the referring physician is competent to interpret and convey to the patient, genetic test results raise unfamiliar problems about probabilities, psychological impact, and reproductive implications.

). Concern about the ability of physicians to interpret such tests for their patients is well founded:

Even though both commercial and academic laboratories are marketing the tests to physicians who lack any expertise in medical genetics, including obstetricians and primary care providers, only a minority of the laboratory directors who responded to the survey said they felt that most physicians can interpret genetic tests adequately for their patients.

Stephenson, *supra* note 15, at 1661 (confirming by study of 4,210 Ohio family physicians). As reported in *The Boston Globe*, based upon a survey of laboratories:

“A lot of people are getting into genetic testing now who haven’t been through human genetics training,” said Dr. Michael S. Watson of Washington

and the novelty of the technology makes providers dependent upon the developers and manufacturers of these tests (both commercial and academic laboratories) for information. This dependency suggests that neither consumers nor their health care providers can reasonably evaluate the technology. Accordingly, until this informational asymmetry between providers/patients and biotechnology companies is decreased through the compilation of clinical data and education, heavy reliance upon market forces like consumer and provider demand is misplaced. In fact, the premature commercialization of genetic testing services may create a general climate of uncertainty that skews incentives for all market participants:

Biotech companies' decisions about what technologies to develop are subject to being inflated by dependence upon them for information, consumer demand, and the influence of consumer advocacy groups;¹¹¹

public demand is subject to being bloated by the aggressive marketing efforts of biotechnology companies that play off of the cultural icon status of DNA,¹¹² the fact that the public is accustomed to undergoing testing for reliable health evaluation and diagnosis, and providers' lack of adequate genetic education;¹¹³ and

University in St. Louis [an official of the American College of Medical Genetics]. "This used to be an unprofitable and esoteric field" when the only genes scientists had identified were those that caused rare disorders. "Now that we are getting into common diseases" influenced by genes—including cancer, heart disease and diabetes—"people are jumping into it."

Saltus, *supra* note 58, at 14. This problem will be exacerbated with the proliferation of genetic testing services. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 23 ("As the number of genetic tests proliferate and their usage expands, primary health care providers and other non-genetics specialists (e.g., [sic] oncologists, neurologists) will play a major role in the provision of genetic tests.").

111. Advocacy groups (e.g., for those afflicted by breast cancer and AIDS) may influence what products are brought to market based upon what they treat rather than their relative quality. See Boyle, *supra* note 13, *supp.* at S5.

112. See Annas, *supra* note 14, at 25.

113. FDA enforcement of its advertising restrictions has had a profound impact on the availability of genetic testing within the United States:

While a number of blood tests have been used in other countries, they have been much less common in the United States. Part of this is the result of Centocor's experience with their test for CA 15.3, a marker for breast cancer. In 1991, the FDA forced Centocor to stop selling this test as a research product in the United States and the rest of the world.

Cancer Diagnostics, *supra* note 84, at 2. As explained above, the precedent set by OncorMed and Myriad is revitalizing this industry. FDA controls on advertising are

providers' decisions to make the technology available may be skewed by fears of legal liability, the desire to appear knowledgeable about and receptive to health care technology, pressure from consumers armed with newspaper and magazine stories on genetic discoveries, and care managers who place severe limits on physicians' time and pressure to maintain patient enrollment.¹¹⁴

Many of the concerns about the commercialization of genetic testing services are familiar and apply to other medical technologies. Nevertheless, (1) the fact that research-stage genetic testing available to the general public is being conducted by private companies rather than by major research institutions, (2) the absence of reliable quality controls on in-house testing services, and (3) perceptions and uncertainties about the predictive capabilities of genetic testing make

circumvented when laboratories and biotech companies sell investigatory services rather than kits. See *supra* note 76 and accompanying text. The relationship between providers and the entities performing these testing services is one-on-one enough to be difficult to regulate. See Boyle, *supra* note 13, *supp.* at S5. Moreover, at least one study has challenged the accuracy of the information provided by genetic laboratories and biotech companies about their tests. According to Dr. Holtzman's study, as interpreted by one of his colleagues who reached preliminary conclusions based upon a sampling of consent forms collected,

several grossly overstate the test's accuracy or represent it in a way that is likely to be misleading. For example, some tests for a single gene did not specify that they only detected a few of the known mutations and therefore would yield an underestimate of the false negative rate. . . . [O]nly half the materials mentioned the availability of genetic counseling to accompany test results. Victoria Odesina and Nancy Press questioned whether recipients even understood the information they did receive.

Meeting Minutes, *supra* note 1, at 2. Some public health officials are also monitoring and documenting the marketing efforts of biotech companies. According to one such account, "[p]rivate companies are performing sophisticated market research studies in order to determine what kinds of new genetic technologies will sell and reap large profits. . . . There are numerous reports being issued to generate investment in prenatal genetic tests." BLATT, *supra* note 21.

114. Providers are especially prone to overuse genetic testing technology in the prenatal context in states recognizing the common-law doctrines of wrongful birth and wrongful life. See generally Belinda L. Kimble, *Wrongful Birth: A Practitioner's Guide to a New Arrival*, 55 ALA. L. REV. 84 (1994) (recognizing a cause of action for wrongful birth); Malinowski, *supra* note 21, at 1497-1513 (demonstrating the need for minimum bioethics standards); Timothy J. Dawe, Note, *Wrongful Life: Time of a "Day in Court"*, 51 OHIO ST. L.J. 473 (1990) (discussing the elements for these causes of action, their application, and relevant state statutes, and providing case citations); see also COOK-DEEGAN, *supra* note 20, at 243 (addressing this potential problem in the context of cystic fibrosis screening); Ellen Wright Clayton, *The Dispersion of Genetic Technologies and the Law*, HASTINGS CENTER REP., May-June 1995, *supp.* at S13-14.

these concerns profound enough to stand alone.¹¹⁵ Specifically, lack of regulatory quality control and the perceived ability of predictive genetic tests to penetrate well into the future despite the absence of PPV makes this testing different. Many consumers and providers are more in awe of the “miracles of modern genetics” than appreciative of its clinical limitations. The demand for predictive genetic testing services may reflect this faith in genetic medicine, a tendency to equate investigational genetic tests with reliable, standard-care diagnostic tests, and the influence of entrepreneurial and academic interests.¹¹⁶ It also may reflect intolerance for health conditions that deviate from the majority.¹¹⁷

The information generated by predictive genetic tests, regardless of its clinical reliability, will deeply impact people’s lives.¹¹⁸ Some of

115. See Silverman, *supra* note 15, *supp.* at S17 (“While the concerns about developing new medical technologies are not unique to DNA diagnostics, genetic analysis has the potential for particularly potent impact on society because of its predictive capacities.”).

116. See BLATT, *supra* note 21.

117. Advocates for the disabled who challenge the availability of genetic testing argue that the concept of “disease” is a social construct. See Marsha Saxton, *Cost-Benefit/Cost-Effectiveness Analysis in Genetics*, Presentation at the Whitehead Inst. for Biomolecular Research (Mar. 30, 1996) (on file with authors). There is concern that genetics testing capabilities could result in less tolerance for deviation from the majority, less appreciation for life, and a general submission to the prejudices of society. Society could be cheated of all that can be learned from those born with disabilities, and genetic testing capabilities will reduce the freedom of choice of prospective parents by putting more pressure on them to abort. See *id.*; see also John Seabrook, *All in the Genes*, NEW YORKER, Feb. 12, 1996, at 80 (reviewing PHILIP KITCHER, *THE LIVES TO COME* (1996)) (“Eugenics is to the science of biology what the A-bomb was to physics.”); Malinowski, *supra* note 21, at 1478-89 (describing how prenatal genetic testing may cause some parents to abort anything less than a “perfect” baby).

118. See generally Andrews, *supra* note 22, at 974-91 (discussing how genetic information, including carrier status, may have a multifaceted impact on people’s lives). As stated by one observer:

Knowing your genetic makeup can also create profound emotional and financial problems. For example, a spouse might use this information in a custody dispute. Or a woman might decide not to have children, for fear of passing on the gene. But if she decides to adopt, will she be approved by an agency? And should a 9-year old girl be tested for the mutation?

Koenig, *supra* note 24, at A23. Similarly, another stated:

The ability to predict late-onset diseases, both common (for example, cancer) and unusual (for example, Huntington’s) can result in dramatic changes in life-style. Premarital genetic analysis can affect the selection of prospective marriage partners, or even whether one will choose to marry. Genetic analysis is already being used for decisions on childbearing or adoption. And in prenatal genetic analysis the prospect of pregnancy termination is confronted directly.

Silverman, *supra* note 15, *supp.* at S17.

those who have opted to undergo the presymptomatic test for Huntington's, a clinically valid test that conclusively determines future onset, have experienced detrimental psychological reactions to the results even when they are negative.¹¹⁹ For those whose results are positive, the suicide rate is approximately thirty-five percent higher than among the general population.¹²⁰ Further, it appears that genetic information already is disrupting the lives of individuals and their families by subjecting them to discrimination from employers and insurers.¹²¹

Although adequate genetic counseling could, perhaps, enable people to cope better with genetic information, genetic counseling is

119. See Andrews, *supra* note 22, at 976; Silverman, *supra* note 15, *supp.* at S17 (discussing market influences on genetic testing); Koenig, *supra* note 24, at A23; Saltus, *supra* note 106, at 14 ("[P]eople who receive good news from a genetic test can be as seriously troubled as those who discover the worst."); see also COOK-DEEGAN, *supra* note 20, at 235-36 (discussing the experience of Dr. Nancy Wexler, codiscoverer of the allele responsible for Huntington's, and her family). Although reliable figures are unavailable, in January 1995 it was estimated that several hundred people in the United States and more than 500 in Canada had been tested for the genetic predisposition to Huntington's. Although the psychological angst condition following testing experienced by those who test positive has not yet been adequately researched, it appears to include the following: (1) "[l]ike lottery winners, people who receive the gift of unexpected genetic health face the quandary of what to do with it"; (2) the results completely disturb conscious and subconscious views of the future which have shaped their lives; (3) though each sibling has an equal chance of carrying a parent's genetic susceptibility to Huntington's, people misinterpret their good fortune as their sibling's doom, and vice versa; (4) having lived their lives anticipating the worst, individuals may experience an identity crisis and mourn opportunities they did not pursue; and (5) all emotional problems blamed on the disease now must be dealt with and family members and friends no longer will make special allowances. See Saltus, *supra* note 106, at 14. As stated by one who underwent this testing:

I don't know who I am or what my goals are The whole world is open to me now. Before, I lived a year at a time; I always had short-range goals. I got my associate's degree, then my bachelor's, then a master's, and I switched careers so I would be working for an employer where I would have good benefits and be protected by federal laws. Now, I don't know what I am going to do—I just know that I'm restless.

Id. To decide whether to take the Huntington's test, Dr. Nancy Wexler asked herself:

"Would I change my job? No, I love what I'm doing. Would I work any less? No. Would I work any more? I am not sure I can. Would I be any less frantic and obsessive? Probably not. Would it change personal relationships and friendships? No. There's an awful lot it wouldn't change. . . . I'm already happy, how much happier am I going to be? Part of me realized how happy I am, being part of this whole research process that's going to make a difference in the future."

COOK-DEEGAN, *supra* note 20, at 236.

120. See Communication between Robin J.R. Blatt and Dr. Patricia Murphy), (January 1997); see also Andrews, *supra* note 22, at 976 (stating rate is four times higher).

121. See Andrews, *supra* note 20, at 984-91; Barash & Alper, *supra* note 58, at 43; Geller et al., *supra* note 58, at 72.

expensive and not necessarily covered by insurance;¹²² the United States does not have enough certified, practicing genetic counselors;¹²³ and health care providers are not knowledgeable enough about genetics to help stretch these limited resources.¹²⁴ Because of poor insurance coverage, costs for investigatory genetic testing are likely to be paid out of the pockets of consumers, and adequate counseling could increase the costs of testing tenfold.¹²⁵ But without mandatory provisions for pre- and post-genetic counseling, the United States is in danger of repeating its sickle-cell screening mistake, multiplied for a whole spectrum of conditions.¹²⁶

Moreover, absent a legal infrastructure to comprehensively protect the public from discrimination by insurers, people may be paying out of their pockets for tests to generate genetic information that gets into their medical records and damages their insurability.¹²⁷

122. Even when counseling is covered, the time constraints placed on genetic counselors under managed care may be responsible for the profession's high rate of burnout.

123. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 4 ("The number of medical geneticists and genetic counselors to whom patients can be referred is likely to remain too small to cope with the potential volume of testing."). At the present time, the National Society of Genetic Counselors has an enrollment of only 1,450 members. See McCormack, *supra* note 18, at 3. Note, however, that some biotech companies are employing counselors to act as a resource for providers. For example, Genzyme Genetics, which has 16 testing labs across the country, employs three counselors. See *id.*

124. See *supra* note 110 and accompanying text.

125. See Michael J. Malinowski, *Capitation, Advances in Medical Technology, and the Advent of a New Era in Medical Ethics*, 22 AM. J.L. & MED. 335, 351 & n.106 (1996).

126. The United States's sickle cell screening program was launched in the early 1970s with good intentions and lots of shortsightedness:

[G]enetic counseling of the individuals tested, and restrictions on the use of the genetic information obtained from the tests, were not made priorities. As a result, the screening generated confusion and anxiety among the population. Many identified as carriers of sickle cell mistakenly thought they were afflicted with the disease. Often, confidentiality was breached, and in some instances, carriers, not actually possessing the disease, were denied health insurance. In addition, because no prenatal test was available, some carriers were told the only prevention for the disease was to avoid having children.

Brom, *supra* note 27, at 129 (footnotes omitted).

127. The EEOC has issued a comment in its Enforcement Manual that prohibits employers from discriminating on the basis of genetic information. See EEOC COMPLIANCE MANUAL § 902.8 (1995); see also *infra* note 263. President Clinton recently signed into law legislation that includes a prohibition against denying a person, previously insured, coverage on the basis of genetic information during a change in insurance. See Health Insurance Portability and Accountability Act, Pub. L. No. 104-191, 110 Stat. 1936 (1996) (nonetheless, not protecting those presently without insurance against genetic discrimination and denial of coverage based upon preexisting conditions); see also *Senate Passes Bill on Portable Health Insurance*, BOSTON GLOBE, Aug. 3, 1996, at A4. Moreover, approximately 11 states have enacted protective legislation, and there presently is a flurry of activity at the state level. See Neil A. Lewis, *2 Marines Who Refused to Comply with Genetic-Testing*

Investigatory predictive genetic tests also may endanger the physical health of patients by creating the possibility of over-treatment.¹²⁸ The

Order Face a Court-Martial, N.Y. TIMES, Apr. 13, 1996, at 7 (reporting that “[o]nly 11 states forbid discrimination based on a person’s genetic makeup” and mentioning that bills are pending in 20 other states). Nevertheless, the danger of genetic discrimination is expanding with the generation of genetic information from the availability of genetic testing. See *Genetic Screening by Insurance Carriers*, 267 JAMA 1207, 1207-09 (1992) (“Insurers may apply genetic information inappropriately. Individual risk will be overestimated if the concepts of penetrance and variable expressivity are not considered.”); Susan O’Hara, Comment, *The Use of Genetic Testing in the Health Insurance Industry: The Creation of a “Biologic Underclass”*, 22 SW. U. L. REV. 1211, 1219-24 (1993) (exploring the potential for discrimination by the health insurance industry arising from genetic testing); *Geneticist Calls for Privacy in Test Results*, BOSTON GLOBE, Sept. 30, 1995, at 3 (“One study found 100 people who were denied insurance benefits because of genetic risks, and a survey of families with inherited diseases found 31 percent had been denied coverage even if they weren’t actually ill”); Koenig, *supra* note 24.

In April 1996, representatives of the insurance industry stated publicly at a meeting of the National Task Force on Genetic Testing that they “would go out of business if they were restricted from having access to genetic information.” Weiss, *supra* note 2. According to some accounts, “Though insurance industry representatives often state that their companies are not likely to use genetic screening now or in the foreseeable future, they demand access to this information concerning their applicants if it is available at professionals’ offices, employment settings, or governmental agencies.” O’Hara, *supra*, at 1220. The insurance industry already has organized to maximize its access to underwriting information. “Currently, seven hundred insurance companies have formed an organization called the Medical Information Bureau (MIB), sharing information about policy holders in an effort to prevent concealment of underwriting information.” *Id.* at 1221. Insurance companies may already be demanding genetic testing. See generally Geller et al., *supra* note 58, at 72 (discussing reports of genetic discrimination); Lee Bowman, *Genetic Inheritance Seen as Privacy Issue*, WASH. TIMES, Apr. 15, 1996, at A10 (According to Dr. Paul Billings of Stanford Medical School, co-author of a study on genetic discrimination,

[m]ore than 900 people known to have a genetic predisposition for certain diseases but without any symptoms themselves said they had experienced some form of discrimination on the job or from insurers, according to the study. . . . Many more people also have been denied life or health insurance for refusing to submit tissue for genetic testing

One response is to flatly exclude genetic information from the insurance process, see *Genetic Screening by Insurance Carriers*, *supra*, at 1207-08, a position supported by the biotechnology industry. See Lisa Piercey, *Kennedy Alleges HIAA Seeks to Undermine Genetic “Nondiscrimination” Provision*, BIOWORLD TODAY, May 15, 1996, at 1. The industry perceives fear of genetic discrimination as an impediment to consumption. See *id.* Such an approach is prudent in the context of health insurance for predictive conditions. We all carry genetic predispositions for disease and, in light of the frequency of which individuals change jobs and health insurance coverage, the genetic predisposition factor is “a wash” for all practical purposes. However, such an approach in the context of life and disability policies (life-long contracts) could price those policies off of the market due to the problem of adverse selection—individuals with genetic information may use it to “cheat” the health insurance market by buying added coverage. *Genetic Screening by Insurance Carriers*, *supra*, at 1208.

128. The importance of specificity (this term is defined at *supra* note 25) in the context of genetic screening tests for cancers is underscored by the fact that the human body can be thought of as “one giant precancer”:

United Kingdom has explored the impact of predictive genetic testing information on the lives of children and concluded that children should not have genetic diagnoses for late-onset disorders.¹²⁹

The precedent set by IVF, Myriad, and OncorMed could carry significant implications for the commercialization of predictive genetic testing services, including widespread commercialization of investigatory genetic testing services. The BRCA testing services offered by these companies may shape standards used to evaluate this technology. If a test has no predecessor, it becomes the governing standard; the most definitive method or test in existence becomes the “gold standard” against which analytical validation is measured.¹³⁰

The availability of BRCA testing services should enable IVF, Myriad, OncorMed, and their research allies to compile enough clinical data to determine predictability in a greatly accelerated fashion. These advantages will pressure other biotechnology companies to make genetic testing available to the public. All of the related science, including sequencing, could be pushed forward, thereby making more therapeutics and treatments a viable possibility. Although such benefits to public health may be considerable, the financial and emotional costs to those who undergo predictive genetic

As it turns out, virtually all of us have precancerous lesions in our bodies. Autopsy studies of women who died of something other than cancer reveal that 39 percent of women between the ages of 40 and 50 have hidden precancer lesions in their breasts—but only 1 percent of women in this age group are clinically diagnosed with breast cancer. Likewise, more than 40 percent of men between 60 and 70 have cellular evidence of prostate cancer that can be found when their tissue is scrutinized under a microscope, though only 1 percent are actually diagnosed with the disease.

Madeline Drexler, *Malignant Predictions*, BOSTON GLOBE, Feb. 18, 1996, (Magazine), at 9.

129. This conclusion was reached by the Science and Technology Committee of the House of Commons and the U.K. Working Party of the Clinical Genetics Society. See Mclean, *supra* note 19, at 120 (discussing recent report of the U.K. Working Party of the Clinical Genetics Society) (citing 1 SCIENCE AND TECHNOLOGY COMMITTEE, *supra* note 50, at xxxviii). The findings of these entities have been summarized as follows:

Where the diagnosis has no direct impact on the health of the child, they suggest that testing, and knowledge of test results, have a number of negative implications. For example, they may lead to the loss of self-esteem, affect the way in which the child is treated in the family or the wider community, prevent a later exercise of autonomy by taking the decision about testing out of the hands of the potential adult, and breach current U.K. policies on the need for counseling before or in the tandem with screening.

Id.

130. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 4-6.

testing during the interim will be significant. At what point does this cost become too high?

The four cornerstone principles of health care are “autonomy, beneficence, nonmaleficence, and justice or equity.”¹³¹ These are inherently individualized concepts, meaning that they lead providers to “focus on the specific patient to the exclusion of other actual or potential patients.”¹³² Applying these principles to widespread investigatory, predictive genetic testing raises many questions. One of the most fundamental is, what should patients be told before they decide to undergo such testing? The danger is that the answer to this question is left to the provider and to the protocol established by the test’s developer, who has every incentive to encourage use to gather both patient data and revenue to cover the costs of research.

The following is a more comprehensive analysis of the commercialization of testing services for BRCA mutations linked to breast and ovarian cancers. First, the prevalence of breast cancer and the approaches taken by the companies marketing these tests are addressed in more detail. Next, the regulatory and general health-policy implications of BRCA testing services are explored through the technique of legal storytelling, which is applied to identify important public health issues (“issue spot”). The varying stories presented embody the perspectives—cancer survivor, genetic counselor, health consumer advocate, and corporate representative—of individuals with personal experiences dealing with breast cancer, BRCA genetic testing, and the R&D, marketing, and regulation of medical products.

III. THE SEMINAL CASE: BRCA TESTING SERVICES

As stated by Dr. Francis Collins, head of the HGP, “[b]reast cancer is the most common cancer among women in the Western world, with a cumulative lifetime risk of 1 in 8.”¹³³ This year alone, 184,300 women will be diagnosed as having breast cancer.¹³⁴ Some

131. Mclean, *supra* note 19, at 117.

132. *Id.*; see also Malinowski, *supra* note 125, at 334-47 (discussing the deontological tradition of medical ethics).

133. Collins, *supra* note 2, at 186; see also Hon Fong Louie Mark et al., *Clinical and Research Issues in Breast Cancer Genetics*, 26 ANNALS CLINICAL & LABORATORY SCI. 396, 396 (1996) (“Breast Cancer is the most common form of cancer in women in the U.S.”).

134. See *From the CDC: Breast Cancer Incidence and Mortality—United States*, 276 JAMA 1293, 1293-94 (1996) [hereinafter *Breast Cancer Incidence*]; David Plotkin, *Good News and Bad News About Breast Cancer*, ATLANTIC MONTHLY, June 1996, at 53, 55-58 (relying upon data provided by the American Cancer Society); see also Dolores Kong, *Mammogram Wars*, BOSTON GLOBE, May 27, 1996, at 34 (stating that, overall, 180,000

44,300 women will die from the disease.¹³⁵ Of the women in whom cancer is diagnosed, 9,200 will not have reached their fortieth birthday, nearly twice the number of women under forty who were found to have breast cancer in 1970,¹³⁶ and another 33,000 will be in their forties.¹³⁷ Breast cancer “is now the leading cause of death for American women aged forty to fifty-five, and causes women to lose more years of productive life than any other disease.”¹³⁸

BRCA testing is available through three schemes, two of which reflect the labeling options under present regulations.¹³⁹ The third entails direct marketing without FDA oversight and restrictions:

For research use only and not for use in diagnostic procedures. NIH is conducting a BRCA testing study in the Washington-Baltimore area that involves 5,000 Ashkenazi Jewish volunteers.¹⁴⁰ Pursuant to this labeling,¹⁴¹ those participating in the study are not given their test results.¹⁴²

For investigational use only. OncorMed has labeled its genetic testing service accordingly. To comply with the accompanying federal restrictions: (1) women must be referred for counseling before and after the test is performed; (2) results must be given by the physician in person; (3) the physician must follow up with the patient about three months later; (4) the test developer must compile data on an ongoing basis to determine which aspects of the gene-testing process need

cases of breast cancer are diagnosed in the United States each year); Richard Saltus, *Breast Cancer Testing: Do You Want to Know?*, BOSTON GLOBE, Mar. 11, 1996, at 25 (“Each year, about 185,000 new cases (4,600 in Massachusetts), and 44,000 deaths are reported.”). For more information, contact the National Cancer Institute, Cancer Information Service, 9000 Rockville Pike, EPN 300, Bethesda, MD 20892. The Institute may be reached by telephone at (800) 4-CANCER (422-6237).

135. See Plotkin, *supra* note 134, at 55, 58 (relying upon data provided by the American Cancer Society); see also Kong, *supra* note 134, at 34; Saltus, *supra* note 134, at 25.

136. See Plotkin, *supra* note 134, at 55, 58. The significance of these numbers is underscored by the fact that malignancy generally grows faster in younger women. Kong, *supra* note 134, at 34. Despite advances in detection through mammography, surgical technique, radiation therapy, and chemotherapy, these advances have not lessened the likelihood that women will die of breast cancer. See Plotkin, *supra* note 134, at 76. “In 1935, 26.2 out of every 100,000 women died of breast cancer. . . . In 1992, the latest year for which figures are available, the adjusted rate of mortality was 26.2 women per 100,000—the same as 1935.” *Id.*

137. See Kong, *supra* note 134, at 34.

138. Plotkin, *supra* note 134, at 58.

139. See *supra* note 64.

140. The recruitment target of 5,000 volunteers was surpassed in just two months. See Wadman, *supra* note 5.

141. See *supra* note 64 (addressing “research” labeling).

142. See Wadman, *supra* note 5, at C3; Weiss, *supra* note 2, at A1.

improvement; and (5) the developer only may charge an amount necessary to recapture the costs incurred for the stated research objective.¹⁴³ Many of these restrictions were developed through an IRB assembled by OncorMed. The IRB was staffed with experts paid consulting fees¹⁴⁴ to develop a protocol for investigational marketing in compliance with CLIA.¹⁴⁵ The sum effect of the work of OncorMed's IRB is that physicians are given a well-developed protocol for their interactions with patients regarding the test, and they are instructed to make the testing service available only to patients with breast cancer or at a high risk of getting the disease.¹⁴⁶ The costs charged for the test fluctuate significantly according to the stated research objective and the testing undertaken. If the company is attempting to locate a specific mutation, the cost may be as low as \$150; if the data is used for sequencing, that cost may reach \$1,650.¹⁴⁷

Independent of FDA Regulations. A BRCA test also is being made available entirely independent of FDA oversight by IVF Institute. IVF Institute offers its BRCA test and the results to any woman willing to pay \$295.¹⁴⁸ Similarly, two of Canada's most respected universities—McGill University and the University of Toronto—are offering open access to BRCA testing.¹⁴⁹

143. See Weiss, *supra* note 2, at A2. OncorMed continues to revisit and revise its protocol. As of January 1997, OncorMed also requires physicians to call in or fax patients' family histories to the company before testing. See OncorMed, Hereditary Breast Cancer Education and Testing Packet (Jan. 15, 1997).

144. See *First BRCA1 Test Hits the Market*, *supra* note 65, at 1-5.

145. See *id.* at 3-5. A summary of the OncorMed protocol is attached as Appendix I.

146. OncorMed is instructing physicians that its BRCA test is available only to certain at-risk patients. See App. I.

147. See *id.* OncorMed offers testing in stages I to III for BRCA1 alterations and stages I and II for BRCA2 mutations. Each stage tests for different BRCA alterations and carries a separate cost—from \$420 for a Stage I BRCA1 test to \$800 for a Stage III BRCA1 test, and \$800 for a Stage II BRCA1 and BRCA2 multiplex test (the tests are done together). See Hereditary Breast Cancer: Questions and Answers for Patients 3, in OncorMed, *supra* note 143.

148. See Wadman, *supra* note 5, at C3 (discussing a genetic test for breast and ovarian cancer); Weiss, *supra* note 2, at A2. Dr. Schulman, who is working in conjunction with IVF Institute, is making the test available to all Jewish women who have been referred by a physician. See Wadman, *supra* note 5, at C3. One of Dr. Schulman's first clients was his wife, who underwent the test at the age of 38, tested positive and had both of her breasts removed. See *id.*

149. See Wadman, *supra* note 5, at C3 ("In last week's New England Journal of Medicine, they report that they are offering on-demand testing for the Jewish mutation."); David S. Rosenblatt et al., *Genetic Screening for Breast Cancer*, 334 NEW ENG. J. MED. 1199, 1199-1200 (1996) (testing for 185delAG is being offered at the University of Toronto and McGill University).

Although the occurrence of breast cancer is epidemic,¹⁵⁰ the fear of breast cancer and the potential market for genetic testing services is exponentially larger.¹⁵¹ Even according to Myriad's own marketing materials, current data suggests that, of all the women with breast or ovarian cancer, only approximately five percent carry a BRCA1 mutation.¹⁵² Of the approximately 185,000 people diagnosed with breast cancer annually, only five to ten percent inherit the disease.¹⁵³ Nevertheless, OncorMed, IVF, and Myriad envision multimillion-dollar markets for their BRCA tests, and their expectations are well grounded. The market for cancer diagnostics is big business, that business is growing quickly,¹⁵⁴ and "surveys of women have revealed

150. See AMERICAN CANCER SOCIETY, *CANCER FACTS AND FIGURES* (1995). Women in the United States have an estimated 10% lifetime risk of getting the disease, and the median onset age is 64.

151. See Koenig, *supra* note 24, at A23 (after the discovery that 1% of Ashkenazi Jewish women carry genetic predisposition to breast and ovarian cancer, "a surgeon who operates on women with breast cancer told me that a day rarely passes when a patient does not ask about 'the gene test'"); Weiss, *supra* note 2, at A1 ("Most important, many women seem not to realize that it is only if a woman has a clear family history of breast cancer—usually identified as two or more close relatives with the disease—that the BRCA1 mutation confers 85% odds of getting breast cancer."). But see Alison Bass, *Ethnicity Called Factor in Patients' Decisions*, BOSTON GLOBE, Sept. 14, 1995, at 3 ("For example, a majority of elderly people of Korean and Mexican descent would prefer not to be told that they suffer from metastatic cancer, while European-Americans and African-Americans would rather know the bad news, the study of 800 nursing home residents found."); Saltus, *supra* note 106, at 14 ("Before the HD test became available, people who were at risk showed strong interest in a predictive test. But when the test appeared, fewer people than expected actually stepped forward.").

152. See MYRIAD LABORATORIES, INC., *supra* note 7, at 2; Saltus, *supra* note 134, at 25 (stating that inherited mutant genes probably account for 5 to 10 percent of breast cancer cases, but this inherited type "seems to be more aggressive; it may also appear earlier than in noninherited cases, sometimes when the woman is in her 20s or 30s"). "About 1 in 200 women in the United States are thought to carry a mutant BRCA1 gene. BRCA1 accounts for about 50 percent of inherited breast cancers, BRCA2, may cause 35 percent, and the remainder are due to undiscovered genes." *Id.*

153. See *The Scientific Questions*, *supra* note 4, at 4 (stating that it is estimated that 10% of breast cancers are due to germline mutations); Hilzenrath, *supra* note 4, at D24 (discussing a news service to detect predisposition to breast and ovarian cancer); Saltus, *supra* note 2, at A18.

154. "Today, the cancer diagnostic business alone is a \$1 billion industry attracting some major corporate players and small companies," and the demand for more reliable ways of detecting and monitoring cancer is growing with an aging American population. See Rosenberg, *supra* note 15, at 80. As stated by a market analyst:

Genetic tests for susceptibility to cancer are a hot area currently, as there have been many announcements of the discovery of genes which predispose some people to specific types of cancer. While genetic tests are done using blood, they are more expensive and difficult than traditional blood tests. Myriad Genetics, one of the genomic companies, has made a decision to enter this business. They are one of the discoveries of the BRCA1 gene, which identifies one form of the

an overwhelming interest in being tested to learn their gene status.”¹⁵⁵ As stated by the National Cancer Coalition, “ready or not, genetic tests are on the threshold of entering everyday practice of medicine.”¹⁵⁶

A. *Meaningful Assessment of the Commercialization of BRCA Testing Services*

Understanding the full implications of commercialization of predictive BRCA testing services is a necessary prerequisite for defining resulting health-policy issues and constructing a regulatory response that maximizes public health benefits. Especially in light of the novelty of this technology, there must be meaningful assessment—in other words, appreciation of innumerable issues and perspectives, many of them contradictory. The potential impact of such law on individual lives, society in general, and the commercial sector responsible for producing health care technology mandates such an approach.

“Legal storytelling” has been defined by some scholars as a license to describe personal experiences without the constraints of traditional legal scholarship, which include an objective tone, extensive footnoting, and reliance upon empirical research.¹⁵⁷ Extremists contend that only those excluded by the legal academy,

hereditary risk of breast cancer. OncorMed is a genetic testing company which also sees an opportunity in cancer testing, and is acquiring diagnostic rights to discoveries made by others. Additional cancer genes will be discovered over the next few years, but the acceptance of such tests will be controversial. Unless the patient will gain some benefit from the knowledge, there is no justification for an expensive test. In some cases, the knowledge that a patient has a high risk of cancer could be devastating.

Cancer Diagnostics, *supra* note 84, at 3.

155. Saltus, *supra* note 134, at 25.

156. *First BRCA1 Test Hits the Market*, *supra* note 65, at 4.

157. See Arthur Austin, *Evaluating Storytelling as a Type of Nontraditional Scholarship*, 74 NEB. L. REV. 479, 485-88, 521 (1995) (stating that feminists and members of the racial critique theory movement profess to speak in a different voice derived from their gender and race experiences, and that they make no pretense of balance or objectivity); Mary I. Coombs, *Outsider Scholarship: The Law Review Stories*, 63 U. COLO. L. REV. 683, 685 (1992) (discussing the rejection of dispassionate objectivity in favor of narrative discourse). For a general and thoughtful discussion of the deontological aspect of the legal storytelling technique, see Toni M. Massaro, *Empathy, Legal Storytelling, and the Rule of Law: New Words, Old Wounds?*, 87 MICH. L. REV. 2099 (1989). See also Anne M. Coughlin, *Regulating the Self: Autobiographical Performances in Outsider Scholarship*, 81 VA. L. REV. 1229, 1231 (1995) (applying autobiographical narrative to legal discourse); Angela P. Harris, *Foreword: The Jurisprudence of Reconstruction*, 82 CAL. L. REV. 741, 750-54 (1994) (discussing how critical race theory utilizes modern narratives in its optimistic moments).

such as people of color and women, have stories to tell.¹⁵⁸ They also argue that reversion to elements of traditional scholarship, such as extensive footnoting, weakens resulting scholarship.¹⁵⁹ Critics of this genre of legal storytelling (the extremist perimeter of “outsider jurisprudence”¹⁶⁰) dismiss such scholarship as anecdotal self-absorption.¹⁶¹ Many pages have been consumed debating whether this scholarship is more or less “real” and meaningful than its more traditional counterparts.¹⁶²

In this Article, the technique of legal storytelling is used to complement traditional-style scholarship. Absent the extensive clinical data necessary to comprehensively evaluate the impact of genetic testing capability on the lives of those who undergo it, legal storytelling is a technique used to thoughtfully assess both the need for and the potential impact of changes in regulatory law. These stories are offered to illustrate the practical effects of the commercialization of predictive genetic testing services. The objective is to engage in legal analysis that is more responsive to the underlying facts and, therefore, more intellectually rigorous and meaningful. Accordingly, rather than a substitute for comprehensive empirical data and with full recognition that its utility is limited by the perspectives of the stories presented, the

158. See Austin, *supra* note 157, at 487 (stating that both feminists and Racial Critique Theory people “claim to get special insights from status as victims or outsiders”).

159. See *id.* at 521 (“The presence of footnotes should not distract from the plot or create static in the flow of the narrative.”).

160. See Mari J. Matsuda, *Looking to the Bottom: Critical Legal Studies and Reparations*, 22 HARV. C.R.-C.L. L. REV. 323, 325 (1987) (recommending a “new epistemological source for critical scholars: the actual experience, history, culture, and intellectual tradition of people of color in America”); Deborah L. Rhode, *Feminist Critical Theories*, 42 STAN. L. REV. 617, 622 (1990) (discussing the experience of women’s actual circumstances, such as being dominated, as a way of understanding feminism). The “outsider” group “encompass[es] various outgroups, including women, people of color, poor people, gays and lesbians, indigenous Americans, and other oppressed people who have suffered historical under-representation and silencing in the law schools.” Mari Matsuda, *Affirmative Action and Legal Knowledge: Planting Seeds in Plowed-Up Ground*, 11 HARV. WOMEN’S L.J. 1, 1 n.2 (1988).

161. See Austin, *supra* note 157, at 491 (“Serious scholars revere analysis and objectivity. To them, subjective advocacy posturing is best left to the *National Enquirer*. Bias is a form of fraud.” (footnote omitted)); see also Daniel A. Farber & Suzanna Sherry, *Telling Stories Out of School: An Essay on Legal Narratives*, 45 STAN. L. REV. 807, 853-54 (1993) (discussing the importance of reason and analysis in legal scholarship).

162. See, e.g., Kathryn Abrams, *Hearing the Call of Stories*, 79 CAL. L. REV. 971, 1021-27 (1991); Austin, *supra* note 157, at 523-27; Richard Delgado, *On Telling Stories in School: A Reply to Farber and Sherry*, 46 VAND. L. REV. 665, 668-75 (1993); Farber & Sherry, *supra* note 161, at 832-38; Daniel J. Solove, Book Note, *Fictions About Fictions*, 105 YALE L.J. 1439, 1439-40 (1996) (reviewing L.H. LARUE, *CONSTITUTIONAL LAW AS FICTION: NARRATIVE IN THE RHETORIC OF AUTHORITY* (1995)).

technique of legal storytelling is used as a means to illustrate underlying facts, identify issues, and analyze public health implications and regulatory considerations.¹⁶³

B. Some Stories

The effectiveness of the legal storytelling technique is dependent upon the selection of stories and the manner in which they are presented. The following narratives are in the words of the subjects who relayed them. They illustrate many of the patient, provider, and regulatory issues identified above in more objective prose. Varying perspectives, both complementary and contradictory, are juxtaposed to stimulate issue identification.

Many prospective subjects were considered, and representative subjects were selected. Interviews with these subjects were audiotaped, transcribed, edited, reviewed by the subjects for accuracy, and revised accordingly. In content, we have selected perspectives resulting from first-hand experience with the issue of BRCA genetic testing. We also have selected arguably contradictory perspectives, such as those of a consumer advocate and a corporate executive from the biotechnology industry. The overall objective was to solicit opinions, based upon personal and professional experiences, on the adequacy or inadequacy of the existing regulatory scheme for predictive genetic testing, with a particular focus on BRCA testing services.

1. A Cancer Survivor's Story¹⁶⁴

In January 1993, at age forty-eight, I was diagnosed with breast cancer. I had a routine mammogram that had a density on it. A six-month follow-up visit was recommended. I elected to ask for a second opinion because I was on hormone replacement therapy, and I knew that this therapy could potentially affect the growth of a tumor if one was there. I went ahead and had a biopsy, and it was positive. So I had a lumpectomy, auxiliary dissection, and radiation therapy. Meanwhile, a decision was made to biopsy the other side. I had some

163. The use of legal storytelling in this Article parallels the storytelling of outsiders. See Austin, *supra* note 157, at 505 ("Descriptions by people like Derrick Bell, Richard Delgado, and Patricia Williams convey the common theme that stories raise consciousness and serve as a vehicle to educate insiders." (footnotes omitted)).

164. This story is based upon an interview with a breast and colon cancer survivor who also is a health care professional.

calcifications which normally wouldn't be of concern but, because I had a primary tumor on the left, a biopsy of my right breast was suggested. In fact, I had a precancer on that side. This was treated with a wide excision. Seven weeks after I finished radiation, I had a colonoscopy and was diagnosed with advanced colon cancer. I had four positive lymph nodes, so I went on to do a year of chemotherapy after that.

I have a very strong history of cancer on my father's side of the family. My father, aunt, uncle, and grandfather had multiple cancers. I have three first cousins who have had cancer, and my brother also has had two primaries. Having grown up with cancer in my family, I have always thought about what's at work in our genetic background. I guess it was always an expectation that some day, eventually, I would probably get cancer. I just never thought I'd get it as young as I did. I certainly never thought I would get two at once. You do think about this when you grow up and are surrounded by it. In a way, it gives you a chance to sort things through and ask yourself, "What would I do if this type of scenario happens to me?"

One of the reasons I remain optimistic despite the likelihood of my having a genetic predisposition is that I believe we are more than our genetic inheritance—lifestyle, diet, and environment all come into play in varying degrees. If you looked at my family pedigree, you would see that all the family members who had cancer lived in or near a paper mill town. Those who lived on the coast were cancer-free. There are also large quartz deposits and, consequently, high radon levels in the paper mill area . . . another carcinogen, along with the dioxin and other byproducts of the paper-making process. So I guess I believe that the bottom-line isn't in yet and that, while genetics are important, there is more to the story.

I had really never thought to myself, "I wish there were a genetic test available so I could find out whether I'm going to get cancer." But I will say that, back in 1989, I became much more aware of genetic testing. I remember saying to my colleagues, "You know this is what my family history looks like . . . don't you think this is a lot of cancer?"

Since my breast cancer diagnosis, I have thought about whether I would want BRCA1 testing—if I would want to know whether I carry the alterations in the gene linked to cancer. I don't know that I would want to be tested for BRCA1, and the reason is that my daughter is twenty-five and my son is twenty-four. As far as I'm concerned, for

me personally, the die is cast. I've had cancer twice. This is clearly my heritage. I know I could possibly have it again. I am probably also at elevated risk for both ovarian and uterine cancer. But I don't know what I would gain if I found out I have an altered BRCA1 gene because I know I would not have a prophylactic mastectomy. I've had my children, and I don't know that my daughter would gain anything by knowing either. Her awareness is already heightened. She will certainly go through pretty rigorous surveillance, seeing the doctor frequently for breast exams, and there's not a lot else she can do in terms of prevention.

Both my kids have asked whether it's possible that they have inherited a gene for cancer. We talk about it a lot. We tend to discuss the colon cancer more than the breast cancer. We have talked about it and, again, I think BRCA1 for my family is probably not as big an issue as the colon cancer gene. I do think I would feel differently about genetic testing for the colon cancer gene for several reasons. If I do have that particular gene, I would then have the option to think about taking an action—such as having a hysterectomy. If I actually had the gene, once again, I don't know that anybody can put numbers on this, but I would be at elevated risk for ovarian and uterine cancers. So for me, personally, that would be something I could do with that information. I can't think of anything I could do with the breast cancer information that would be any different from what I'm doing now.

I think risk is a lot like beauty. It is in the eyes of the beholder. Perhaps because I've grown up in a family with various, multiple cancers, and my family members have dealt with it and gotten on with their lives, my perception of risk is maybe a little different than someone else's might be. I don't know that I could say how I would feel if I had a strong family history of breast cancer. If my mom or sister had breast cancer, I suspect I'd feel a lot more threatened than I do now. I would probably also feel more threatened in terms of my daughter. In my opinion, undergoing this type of testing is a very personal decision.

I think the whole area of predictive genetic testing is something that we need to address, because we're going to have a lot more genes coming down the pike. There are going to be many people who are going to be affected by earlier diagnosis, and all these discoveries that are coming . . . it just means that there are that many more people at risk who are going to face these issues and be anxious. I also think one of the unfortunate down sides of genetic testing is that, for the

average person, it is extremely difficult to sort out where you fit into this picture . . . if you fit in at all. While there are high-risk cancer clinics at some major teaching hospitals and research institutions, not everybody has access to these kinds of services. Not everybody lives in a metropolitan area.

It's interesting that, although the BRCA1 testing is still relatively new, independent labs are giving out results. I think it's potentially dangerous to offer predictive genetic tests without stringent quality control and regulation. Giving out results that aren't accurate isn't the whole problem. Based on my experience working with researchers who are extremely careful, even when they set up programs with many safeguards, the issues that arise for people are still traumatic. This type of genetic testing is not something to be taken lightly. My personal bias is that this kind of testing must be set up by the medical profession, ordered by the medical profession, and that members of the medical profession should be the ones responsible for giving out the results—not independent labs or companies developing the tests. I mean, if you go to your physician and you have your annual physical exam, and you have a chest x-ray or a blood test, the lab doesn't call you and give you your results. I really feel that there should be the same kind of oversight and development of medical standards for genetic tests that there are for other types of medical tests, perhaps even more so. A lab shouldn't be doing genetic testing if it hasn't gone through an approval process for that particular test.

There are so many things that one needs to know before undergoing genetic testing. I think one of the biggest challenges of the genetic revolution is the dissemination of information and education of both the primary care providers and the patients themselves. It's very tough to sort out all this information. I think it has created a great deal of concern and a lot of anguish for women who probably aren't even at risk for the inherited form of breast cancer. Women almost always overestimate their risk.

From a cancer patient's perspective, what I believe is most needed for an individual prior to this type of genetic testing is time, especially time for genetic counseling. There also needs to be coordinated peer support so that when an individual is diagnosed with cancer, no matter what type it is, they can, through their physician, nurse, or social worker, say, "I would really like to speak with someone who has been through this decision-making process." The other issue that concerns me is the point in time that genetic testing is

discussed. If it's close to diagnosis, you are concentrating on how you are going to get through the surgery, whether you are going to live through the treatment, who's going to take care of your kids for five days a week during seven weeks of radiation, and what's going to happen with your job. That's enough for the average person. There's a limit to how much you can deal with at one time. We need to think more about when people are mentally ready to hear the information on genetic testing and its implications.

I have spoken with many people with cancer over the last few years. I also have had the advantage, if you want to call it an advantage, of not only talking with people and growing up in a family with a lot of cancer, but also working in this research area. And even having dealt with this every day, the decision to undergo genetic testing still takes a lot of thought. You have to know what the ramifications of that decision are and, let's face it, there are a lot of potential ramifications. How one perceives the risk of the ramifications is as important as how you perceive your risk of the disease. For example, the thought of being without health insurance, particularly if you have children, or the thought of being denied employment because of something like this is frightening to most people, and right now these are very real potential ramifications.

One of the issues I came up against when I visited my gynecologist for my annual exam after I'd been through both diagnoses was insurance coverage. We discussed the fact that I might be at elevated risk for both uterine and ovarian cancer, and what strategy we would take on this. He suggested my having a baseline transvaginal ultrasound. I agreed that I would have the baseline ultrasound and the other baseline test recommended, which was a blood test called CA125. My insurance carrier refused to pay for the blood test. Just on general principles, I decided I was going to argue about it. So I called my doctor and told him what the insurance company said. Essentially, they said it would not affect patient care, and that's why they wouldn't cover it. So my doctor wrote a blistering letter saying it absolutely would affect patient care, explaining how I was at risk and that very positive action would be taken if this value was elevated. They covered it but made it clear that they were going to pay for this once and only once. Since then, I do go for a visit every six months and have a pelvic exam, but I'm not doing routine ultrasounds or blood tests. I could do it if I wanted to, and pay for it

out of pocket, but I just don't feel that is something I choose to do right now.

What it boils down to for me is, "Am I going to go and ask for a hysterectomy if I have this colon cancer gene?" I don't know about that answer today. I've had a long time to think about this. I know a lot, and it's still very difficult for me. So can you imagine the confusion for the average person who, out of the blue, develops cancer or learns someone in their family has it? Right now, the colon cancer gene testing is at a stage where they're verifying their results to be sure that they have completely reproducible results. Results are not yet being reported to patients. I have had my blood drawn and provided tissue samples as well. I will be notified when a clinical testing program for colon cancer is available, and I will make a decision about testing at that time.

In general, I support all the research taking place on gene susceptibility testing. I think that the quality of most of the research is good, and those researchers working in the area don't take any of these issues lightly. But I do think that this type of testing must initially take place in a research setting, to see what the ramifications are, to work out the kinks, before opening it up to the general public. It will be interesting to see who hops on this particular bandwagon. I've heard about the marketing of predictive genetic testing for breast cancer second-hand, and I think that's pretty unconscionable. I know how volatile it is for people to think about genetic testing. If it takes place outside a setting with a lot of education and counseling, well, I just think it's unconscionable to do the test and give out the results. I don't know that there will be any way to keep track of what the results and the outcome will be. I think that's the other very bad part about genetic testing for breast cancer. Are companies going to keep any kind of records? Are they going to do any kind of reporting? What about doing further testing on samples? Who will have access to the test results? Who will be there to help individuals deal with the information they receive? There is no doubt that safeguards need to be put in place, immediately, before it's too late.

2. A Genetic Counselor's Story¹⁶⁵

Our center is involved in a number of clinical research projects to offer general predictive genetic testing to anybody in the local area

165. This source is a genetic counselor at a major medical research institution.

who may have a mutation in a cancer susceptibility gene, BRCA1. One is a general research protocol that allows us to draw blood on anybody who has cancer to look for an inherited factor. We consider it a fishing expedition, and it has a pretty low yield. In another program, one of our predictive genetic testing programs for breast cancer, we only test people who already have a known mutation in their family, so we're starting with knowing exactly where in their genome to focus. In this program, we use a three-visit model with extensive counseling because it is too much to give all of the information necessary in one visit. We do not do counseling by phone, so individuals who are out of state are referred elsewhere for counseling and testing. We use a networked group of counselors that are trained and specialize in cancer genetics.

I'm not aware of any of our researchers having financial ties with the laboratories performing BRCA1 testing. I really do not think there are any financial incentives among the researchers within our institution. However, since our laboratory does not have CLIA approval to perform testing at this time, we have agreements with other laboratories that are certified to confirm all results independently. So everyone who comes to our program has two independent tests done on their samples. Two samples of blood are drawn, and one tube is immediately sent out to the other laboratory. This offsets concern about a coding error or contamination at the beginning of the process.

In addition, in a separate testing protocol, we have an agreement with a specific biotechnology company. They will perform the entire sequence of BRCA1 free of charge and we will provide the pre- and post-counseling. We are one of nine centers with whom this laboratory is collaborating on this project. It is with the understanding that they will be allowed to use that data to determine the sensitivity and specificity of their test assay. Before a lab can offer a test for clinical use and charge for it, and before developers can do clinical marketing, they have to prove that their analyses reach a level of specificity and sensitivity that's acceptable. And so we're helping them do that, basically. This is a time-limited study. Right now, all the people who undergo BRCA1 testing through our program receive it free of charge since it is part of a research protocol. Very soon, the commercial labs will be offering testing, and there will be a charge for the laboratory costs.

The women who come to our BRCA1 program are either concerned about getting breast cancer or actually have breast cancer.

A lot of those concerned have a family history of the disease. As a result of the publicity about BRCA1 testing in lay press journals or newspaper articles, we have recently received a flurry of phone calls. We also have a cancer risk and prevention clinic at our hospital that attracts a lot of inquiries. Many of the women who decide to be tested do so because this is an area of uncertainty that they've been living under. A lot of these women see this as a way of getting control—they really want to know, and that's a lot of what it comes down to. We also see people for second opinions.

The majority of patient referrals come from outside providers, such as doctors and genetic counselors. Although we have the ability to search medical records here at the hospital to find people who might be at risk, we don't. In fact, even for people who come into the cancer risk and prevention clinic or who are at the hospital, special permission is necessary for us to obtain their records. The oncologists at the hospital know about us so, if they have a breast cancer patient who says, "Yes, my sister also had breast cancer at the age of forty," then it's very common that the oncologist will suggest to the patient that they contact us. Whether an individual with breast cancer follows through on this depends on the person themselves. Some people want to talk soon after diagnosis, others really have no interest in doing that at that point.

The people who are eligible for genetic testing are those with significant histories of breast or ovarian cancer, meaning that they have three or more people in their family with the disease. It is important for the family history to include more than one generation and premenopausal cases of breast cancer. And they need to have a living affected family member that we can test first because, following the classic genetic model, we need to start with somebody who we assume has the disease. Otherwise, if the results are negative in the healthy person you're testing, you don't know if you've even looked at the right gene or the right place on the right gene. So we make a very big deal about needing to first test somebody who is affected with the disease and has had their diagnosis confirmed with medical records.

The only exception to that now are Jewish women who have significant histories of breast or ovarian cancer. For these women, we offer testing for the three known mutations without testing an affected relative first. Part of what we are currently doing is mutation testing for the three common mutations in the BRCA gene that occur within the Ashkenazi Jewish population. I am familiar with the controversy

surrounding the notion of a “Jewish gene for breast cancer.” I think that, if there is malice in targeting a racial group, it’s very wrong. But I don’t think that’s the case with BRCA1. This is not the first time that ethnic backgrounds have been important to think about in genetic research.

What has struck me most in thinking about our predictive testing program is that we’re starting with people who themselves have had cancer . . . they are the entry point into the family. These people understand that, really, their daughters and sisters are the ones who potentially have the most to benefit from this. These are people who have already had their cancer. We began offering testing with the assumption that an important reason why people who had the disease would want to be tested would be to get the explanation of why they got cancer, and that they already would be assuming that they carry an altered gene. What we found is that cancer patients we have seen are really much more tortured about the possibility of being a gene carrier and the possibility that they might in fact have higher chances of getting a second cancer. I’ve talked with several people now that have ultimately made the decision not to go forward with testing because the idea was so distressing to them that, despite the fact that their sister was really pushing them and wanted to know. When this happens, I tell the person “Look, you’re the one that has to decide because it has direct implications for you. It’s okay to make the decision that is best for you.” So this has been eye-opening. BRCA1 testing does not provide benign information even for somebody who’s had cancer. It is not an easy decision to make.

You can appreciate then that getting other family members to provide samples for BRCA1 testing can be complicated. When you deal with families, you encounter all kinds of different situations. There have been situations where the person in front of you says, “There’s no way that my aunt with cancer will agree to do this . . . I can’t even ask her.” In this case, you are really stuck. You can’t offer anything. So there are certain instances where a person is the gatekeeper for the family, and, if that person does not want to participate at any time, we can’t offer anything further. There have been other situations where somebody will initially be interested in participating but then change her mind. We honor that. There’s another situation that doesn’t come up as often, but it has happened. The person sitting in front of you says, “My cousin has had cancer,” we’re put in touch with that person and she becomes very enthusiastic

about participating, and then the person you have been directly dealing with says, "I don't want to hear any more about this." But, by that time, we're already working with other people in the family and will continue to work with them.

Incidentally, we don't tend to see many husbands or fathers coming to the counseling sessions with the women considering BRCA1 testing. We see a lot of friends, sometimes family members, but that gets complicated because family members may also be at risk. You wonder how much they are acting as a companion and how much they are focusing on their own stuff. Mainly, women come by themselves. We do encourage women to try to bring somebody when the results are given.

All participants receive a patient information sheet that we've put together about the genetic testing program itself and another just about the BRCA1 gene and what we know about it. Because our program is a research program, there are three consent forms: one to enroll in the program, a second to have blood drawn and analyzed, and a third to receive results. The initial consent form is mailed to patients before they come in for their first visit, and they are asked to bring it with them. There's a lot of information in the consent form that can be looked at beforehand. Women are asked to sign the first consent form during the first visit, and then at the end of the first visit we'll show them the blood drawing and analysis consent form. They can either sign it that day, or they can take it home and think about it. The informed consent process is integral to our research. All patients that participate in our testing program are told that this is part of a research protocol, and that they must sign an informed consent document.

Much of the same information is reiterated for all three of the consent forms. We talk about the implications of results. We talk about the fact that, if there is no mutation, the person's risk is lowered down to that of the general population. Having a gene alteration would substantially increase the risks of cancer. We also mention the pros and cons of testing, including the possible stigmatization of knowing that you have an altered gene. Insurance concerns are something that are heavily emphasized. We discuss the possible strain on family relationships, and we talk about the fact that there is no known medical benefit to being tested.

For some people, there are other definite benefits. It may be that the person needs this extra information to put them into gear to have surveillance done. People have told us that they think knowing they

have an alteration would motivate them to plan better, to take better care of themselves. Now we're looking at the outcome in terms of behavior. I'm not sure anything changes human behavior, but there are people who think it will motivate them. Also, a lot of the women who want testing have daughters—that is a big reason for wanting to be tested. They say "For myself, I don't really care, but I really am so anxious about my daughters. I really want to know for their sake." If the woman has the altered gene, then her daughters have the option of being tested. If the woman doesn't have it, then her daughters are not at risk for inheriting it.

Providing the results of BRCA1 testing is one of the most difficult aspects of my job. It is very powerful information. There has to be a lot of thought put into it beforehand, and a lot of follow-up and TLC (tender, loving care) afterwards. Giving the results can really be very involved, depending, of course, on the person being tested. For some people, it takes twenty minutes. That's all the time they want to give us. They just want to go home and let it sink in. Some people are very private and, whether they are devastatingly sad or overwhelmingly happy, they don't choose to share that with us. That's why there is a third follow-up visit. Other people have a million and one questions or they want and need to express their emotions and, for them, it can be an hour-and-a-half to a two-hour session. We have set up our protocol to call in a couple days after giving the test results. If we're really worried, we'll call them that night. If we are not so worried, we'll wait a couple days and then we'll check on them. There have been instances where a husband or other companion has come in with the woman when it is time to receive results. Some are very supportive, others are not as helpful.

The results are given to the person verbally along with a letter that addresses all the things that we mentioned—the implications of the results, what it means and doesn't mean, what the concerns are, and the letter stresses that they can always contact us again. Even if they can't remember what we told them, they have the letter to refer to. And I tell them that they can either throw it away if they are worried about having something with their name and results on it, or show it to their health care provider, or stick it in a file somewhere in their house. The control is up to them. We don't document results in medical records. The results will be told to the other providers in our high risk clinic who know not to write it anywhere. Outside our little close-knit group, the providers are not told. We are more than happy to disclose

the results if we get written permission to do so, but otherwise it doesn't go anywhere. It is unlikely that an insurance company would learn about the result because it is completely done in a research setting.

Because this is powerful information, we have to consider whether someone will be suicidal after hearing the news. We had one case where the woman was very upset that she got a normal result (not in the BRCA1 gene, but in a different cancer gene). She was hoping for abnormal results as her way out of her horrible life—being able to get cancer and just die. Us telling her, “No, that’s not going to happen,” was not good news for her, so for her we were worried. But I think, in general, we are more concerned about the people who get an altered gene result. They have filled out some psychiatric assessments and had a lengthy discussion before the day results are given. So hopefully we have an idea of their stability and emotional well being before they even get to this point. It is an important reason why we have a clinical psychologist working on the project.

I generally do feel comfortable giving out the predictions of breast cancer risk because of the way that we do it. We’re deliberately vague. I am amazed when I hear that somebody says, “Okay you’re forty. By age forty-five, you will have this risk, and at age fifty your risk will be that.” We just don’t know that for certain. We’ll give ranges, but often we downplay the numbers. Remember, for most people, numbers don’t mean anything. You could give the same number to four people and they will all perceive it in a very different way. For many women in the breast cancer clinic, they are living with so much feeling of doom and fear that they already know they have a higher risk of cancer. In fact, for a lot of people, they’ve over-estimated what their lifetime cancer risk is. So I’m not sure that they even hear me when I say, “Look, your highest risk is fifty percent.” Now, for me or you, that sounds like an incredibly high risk, but for these people, that’s quite a drop in what they already think their risks are.

Sometimes I think that being part of this research is a scary place to be because there are not a lot of models for what we’re doing. We see other institutions doing things in ways that we don’t agree with so we can see what it is we don’t want to do, but it’s very hard to know how best to do things. For example, I hear from other centers that have just gone ahead and started doing this type of testing more freely. I know that there are a few labs that are offering predictive genetic

testing for breast cancer without a required counseling component. There are a few labs where you can just send money and a blood sample and the test will be done. There's at least one site that will take anyone's blood, regardless of whether they have cancer or a striking family history. A couple of these sites strongly encourage counseling, but I don't know if it's required.

Whenever you work with families, what works for one family doesn't always work for another, and so you are constantly reevaluating how you're doing things. The first step in our testing program is to send an invitation letter to families saying "You know, this altered gene may be in your family. Do you want to know about it?" Well, one person is going to call and be upset that we didn't give more information in the letter—"As you know, I've been seen in your center for five years. This is all you can tell me? What do you mean that I have to have another blood test? You already have my blood." And then a second person will get the letter and be devastated by what they are reading into it. So it's hard to know how much information people really want, and it's hard to be able to predict that. If there's one thing we've learned, it is that you can't predict how people are going to react to this information or what people are going to want to hear.

I have confidence in our approach to predictive genetic testing for breast cancer because we do everything within a group process. We have people with specialties in oncology, psychology, and genetic counseling. We also have set up an outside ethics group for our research protocol composed of people not affiliated with the hospital so that, when we really get stuck or we've done something and we want reassurance that it was okay, we can go to them. We meet a few times a year and go over the case histories and how we've resolved it, or how we plan to resolve it, and they give us their feedback. I think it's really useful, because we do a lot of obsessing about things. Also, you can get to a point where you're convinced that you're doing the right thing, and sometimes it's really important for an outside group to look at it and say, "Well, what about doing it like this instead?" This is important because people do tend to think alike after working together for a while.

From a laboratory standpoint, I think there has to be some sort of standard to ensure accuracy of the results. Still, it worries me whenever the word "regulation" is raised. Are we going to make it difficult, actually impede our ability, to do genetic testing? I think

there is a fine line sometimes when it comes to regulations. Do we regulate each genetic test that comes along? Do we just regulate the labs? There are a lot of things to consider

3. A Consumer Advocate's Story¹⁶⁶

As a statewide consumer advocacy organization, our mission is to increase breast cancer research funding, improve access to breast cancer care and treatment, and foster consumer participation in research decisions. Although we are always pleased to see that researchers are looking for the causes of breast cancer, we are seriously concerned with the trends in genetic research. There has always been some concern in our organization about the genetic factors at play in high-risk families. However, only five to ten percent of women who get breast cancer have a strong family history; most have no identifiable risk factors. The way in which Jewish women are being recruited for predictive genetic testing is alarming. BRCA1 is now being referred to as the "Jewish gene," and this incredible focus on one particular ethnic group, especially without education and the support of the community, is appalling.

The way in which genetic research is being portrayed is very distorted. There seems to be this implication that if you have a test, and it shows that you have an altered BRCA1 gene, you can do something about it. That is not the case; there is still no known proven intervention for breast cancer. Our organization has received many calls about breast cancer genetic testing over the past year. There have been many people who are initially very excited about it, and say that they want to go out and get tested. But when they learn a little more about what this type of testing can and cannot tell them, they realize it may not be so great. First of all, it may not tell them anything that would be actually useful to them. And, psychologically, it can be extremely distressing to them and their families. Furthermore, there is no protection from discrimination. I think, these days, everybody understands how precarious health insurance is and that if you were to be diagnosed with breast cancer, or found to carry an altered BRCA1 gene, you run the risk of losing your insurance, even your job. There are many people in our group who make serious life decisions based

166. This story is based upon an interview with Jan Platner, J.D., who is the Executive Director of the Massachusetts Breast Cancer Coalition (MBC). MBC is located at 85 Merrimac St., Boston, MA 02114. Ms. Platner may be contacted by telephone at 800-649-6222 or 617-624-0180, or by facsimile at 617-624-0176.

on the fear of discrimination. The other concern is that most causes of breast cancer are not inherited, but occur sporadically, possibly as a result of environmental influences. We are very concerned about the focus shifting from the environment almost entirely to genes.

All that really exists now is data. I think that we are in an age where people place a high value on information. I'm not sure it's knowledge; it's just information. We are a culture that reveres knowledge and that thinks that science has far more answers than it probably does.

It is our position that predictive genetic testing for breast cancer is still experimental and academic. Whether a woman wants to have such testing is an extremely complex decision that needs to be made by the woman herself and her family. It's a very personal decision. But we believe that no one should even contemplate this unless they have up-to-date information and appropriate counseling. Also, nondiscrimination and confidentiality protections are needed for people who decide to be tested. It is our position that no genetic testing should take place whether in clinical trials or commercially without these protections in place. But this is not happening. Right now, for example, anyone could walk into some of the local hospitals and get tested for BRCA1. All they need is to be able to pay for the test. It concerns me that this type of testing is being offered in some settings without professional counseling. Very soon, wide-scale testing will be made available. The majority of health care professionals have little knowledge about the research status and ramifications of this type of testing and little, if any, experience in genetic counseling.

It also concerns me that, through commercially available testing, people are getting information from the companies who administer the tests. There have been some pretty aggressive marketing campaigns and literature sent out to recruit people in a way that is problematic. For example, there is marketing to encourage all Jewish women to get tested. You can even do it by mail order—by sending in a blood sample and \$295 to one lab in the country. The bottom line is that the companies have a tremendous financial interest in creating a new market for this product. And some researchers involved in this area have personal financial interests in the companies. Because I'm a lawyer, I may be more sensitive to the notion of conflict of interest. At the very least, there should be some rules regarding disclosure. We also know that one of the companies is marketing its testing service to

disease management facilities and insurance companies that would benefit from information about a person's risk for breast cancer. With the facilitation of computerized access to medical records and the lack of consumer protections, this is *incredibly* problematic.

The other major concern of our organization is that gene testing for BRCA1 seems to not be regulated at all. We have met with the State Attorney General's Office and their Consumer Protection Division and Civil Rights Division to talk about these issues. It's problematic, because the resolution of this kind of issue usually occurs at the federal level. It is my understanding that the FDA could regulate this, but they don't since it's not a pharmaceutical and not a medical device. Although the FDA is not a perfect agency and its regulatory powers are being cut back, I think it is critical that they have strong jurisdiction over this. I don't think industries should ever regulate themselves. This information has the potential to impact individual lives in so many ways. Inadequate regulation is a serious public health issue that needs to be addressed.

The issue of informed consent for participating in these studies also is a great concern. I have reviewed a number of informed consent documents that are being given to women. The majority of these documents are inadequate, even the ones developed for clinical trials in large, well-respected institutions with people who are sensitive and knowledgeable about these issues. We have no idea what happens to people when they get test results, be they positive or negative results, or if they have any understanding of what this means to them or for their family members. We have talked with a few people who have been tested who entered the process understanding the issues and who were surprised at how they were emotionally impacted by the test. They thought they were prepared but later admitted they really were not. And the family issues created by this type of testing are overwhelming. One woman was tested within a clinical protocol and wanted the test to be blind; she didn't want to know the results. But after she was tested she received a letter from the facility basically saying, "We have some bad news for you . . . you are at high risk." She was strictly doing this because she thought it would be a contribution to science. Then she was faced with the decision of whether to tell her daughter. Although some of the research programs have a psychologist and psychiatrist on board and apparently make an attempt to help sort through the issues, it sounds like it's just an

attempt. Many women considering testing feel that these programs still have a long way to go.

Ruth Hubbard¹⁶⁷ has a great analogy—she says that if you want to build a skyscraper you turn that task over to architects. But if you want to decide *whether* to build the skyscraper, those are not the people who should make the decision because you will get the skyscraper no matter what. Consumers really need to be part of the dialogue before genetic tests are developed.

4. A Corporate Representative's Story¹⁶⁸

I work as the education and corporate communications manager for a national genetic testing company with a very large research and development arm, genomics group, and clinical trials lab. At our company we do prenatal testing as well as molecular and biochemical testing. We also do cancer cytogenetics and provide a number of other genetic laboratory services.

Within our clinical trials lab, we are currently working with a number of collaborators in the area of BRCA testing. We were not involved in the cloning of the BRCA1 gene. However, we do develop tests for certain genetically inherited diseases, and we have the capability with some new technology that we developed to run clinical trials for academic partners. We also are very much involved in the development of protocols for the delivery of this type of predictive genetic testing service, including genetic counseling, which has to be part of BRCA testing. Although protocols for testing are generally developed by professional medical organizations, we believe that we have the experience and the data to help these organizations as the BRCA test becomes available. We develop the protocols for use in conjunction with our academic collaborators who will be the ones who actually make them available within the physician community. There's a lot of information that comes forward during a clinical trial . . . it's not just the mechanics of putting something through the testing process. We address the many ethical and social implications that arise from the testing process itself prior to introducing a new genetic test.

Our laboratory does not accept specimens from physicians or consumers interested in BRCA testing. The specimens that come

167. Ruth Hubbard is Professor Emerita of Biology at Harvard University.

168. This story is based upon an interview with an executive at a major biotechnology company.

through our lab come only from our collaborators, and they are all research studies. We have chosen not to make this test commercially available at this time because there are too many unanswered questions. The protocols for the use of this test have not yet been established, and we believe that its entry must be done carefully. The development of a predictive genetic test is a very touchy issue, one that needs a lot of examination and care in the thought process prior to its entry into the market.

As an example, an important part of any genetic test is the protocol for providing test results. The findings and report process have to be explained very carefully to a physician. We do not just provide physicians with a written report that states that the patient has tested negatively or positively. With genetic disease, there can be familial and psychological impact, and a lab cannot just print out a report and send it off. The interpretive process is one of the most important things on any report that comes out of a genetic diagnostics laboratory. As part of our work, we are examining the way in which BRCA test results ought to be provided and the type of counseling that may be necessary to deal with the impact of the information.

An illustration of how well the genetic diagnostics community works together is what happened when the genetic test, by linkage analysis, for Huntington Disease (HD) first became available in the early 1980s. A consortium was formed of academic and commercial geneticists and others who got together expressly to carefully map out the process for the manner in which testing should be offered. When the gene was uncovered in 1993, these guidelines were only intensified. HD still is not offered to anyone except through a carefully controlled clinical protocol. All of our patient samples, for all genetic tests, come from referring physicians—not directly from consumers.

I have seen one package of marketing literature on BRCA testing from one company offering the test. The materials do not appear to be very unusual. In fact, I was delighted to see how responsibly and sensitively they have been handled. The companies that are announcing and marketing this test, I believe, are now working through IRBs that have been established within their own companies. There is still much to be determined before this test is made widely available.

I think, as a whole, the genetics diagnostic industry is very cautious about what tests it offers and how they are offered. In my

view, the commercial industry is equally as cautious and conscientious as the academic centers. I think the genetic testing industry does a very good job of regulating itself. We have a number of organizations that inspect and license our laboratories. These inspection and licensing procedures involve a wide range of quality control and assurance issues and standards that we are required to meet. CLIA, the College of American Pathologists (CAP), the Association of Certified Medical Geneticists (ACMG), and state licensing agencies have stringent rules and regulations, and our labs are licensed by all of these organizations. I do not think it is necessary for the genetic diagnostics industry to be regulated by the FDA.

To my knowledge, no genetic test has to be approved by the FDA, and there are no FDA guidelines or approval processes on any genetic diagnostic test. The labs that develop these tests have very rigorous programs of their own. We would not offer any kind of genetic test without a large amount of data showing efficacy, sensitivity, and specificity. I don't think there is a need for any additional external review. Any genetic testing company would be foolish to introduce a test that wasn't technically sound. Think of the potential for harm, the liability issues, the damage to a lab's reputation, and so on.

Our president presented testimony to the Senate Cancer Committee on the issue of regulation in late 1995. The Executive Summary states our position on external regulation:

The dawn of a new era of testing for genetically-based disease is both exciting and challenging. The prospect of being able to identify individuals at increased risk of cancer and other devastating diseases—and thereby facilitate prevention and earlier, more effective treatment—could reduce human suffering to an extent that is unprecedented in medical history.

Our collective efforts towards this goal must be conducted with great care. The evolution of genetic diagnostics is an interactive process that needs a high level of flexibility to cope with constant change. Test validation, laboratory performance, and genetic information must all be addressed in appropriate ways, but excessive Federal regulation must be avoided.

Any framework for validating new genetic tests must reflect a diversity of issues. For instance, testing for a disease that is caused by a single genetic defect, like Huntington Disease, raises different validation issues than testing for cancer, which may involve many genes. Our approach to validating such tests must be flexible or it will

stifle progress and prevent generations of useful information for patients.

Placing additional regulatory requirements on the process at this time could undermine the investment required to make these potential clinical benefits a timely reality. Existing voluntary collaborations between commercial and academic laboratories and researchers work well and have successfully moved tests like those for cystic fibrosis (CF) and Huntington Disease (HD) into general use. Cancer testing is more complex but can be managed in a similar way.

Genetic testing laboratory performance standards are regulated by the College of American Pathologists (CAP) and the American College of Medical Genetics (ACMG) under the Clinical Laboratory Improvement Amendment (CLIA) of 1988. Additional regulation of lab performance is not necessary.

Increased education in genetics for primary care physicians and other health care providers is crucial to the understanding and appropriate use of genetic tests, but adequate resources do not currently exist. This is an area where the Federal government can play a useful role.

Finally, insurance reform, including elimination of pre-existing condition exclusions and elimination of lifetime caps, will remove major limitations to the effective use of genetic diagnostics. Congress should address these issues in pending health care reform legislation.¹⁶⁹

I am not saying that genetic testing should not have *any* kind of regulation. But I think it can be imposed upon the community to do some major self-policing. Perhaps certain additional criteria could be met through the existing regulatory processes (CLIA, CAP, and so on). But to have the FDA involved in genetic testing would slow the process unbelievably.

Our market analysis for BRCA shows that there is certainly a large potential market. However, an additional reason for not offering BRCA testing is patent ownership. To date, there has been no indication that patent filers are willing to license out for commercialized diagnostic testing.

By the way, the academic institutions charge for their testing. So there really is not much difference between us, except that officially we are for-profit and they are not, although some of them actually are. The major difference is in how services are marketed and how the two entities are perceived out there in the marketplace. One of our larger competitors is an academic lab that charges for services and markets

169. Statement of Elliott D. Hillback, Jr., Pres. & CEO of Integrated Genetics Laboratories, Inc., before the Senate Cancer Caucus (Sept. 29, 1995).

their tests much more aggressively and directly to physicians than we do.

IV. UNIFYING THEMES AND DIVERGING THEORIES ON REGULATION

The preceding stories are linked by an overarching theme: the commercialization of predictive genetic testing services essentially is being left to market forces, academic interests, and the judgment of primary care physicians. Beyond this basic message, however, the stories raise an entanglement of issues and present disagreement about what, if anything, constitutes the appropriate regulatory response to the commercialization of predictive genetic testing services. The following is an effort to sort through these conflicting opinions and draw upon the discussion set forth in Parts II and III, to present arguments for and against direct regulation of predictive genetic testing services.

A. *Continued Deference to Market Forces*

Advocates of regulatory restraint support maintaining the status quo. One of the strongest arguments in favor of this position is that IRB review coupled with the incentive to avoid product liability is effective—as made evident by OncorMed’s extensive protocol (attached as App. D). The regulatory effect of legal liability must not be underestimated, for biotechnology executives are well aware that circumventing the FDA review process sacrifices the liability limitations associated with the MDA.¹⁷⁰ Under this view, the fact that

170. See *First BRCA1 Test Hits the Market*, *supra* note 65, at 4 (“Since FDA does not regulate genetic tests, OncorMed and the companies that will follow it encounter few regulatory barriers. However, by the same token, their products do not receive the certification of safety and efficacy that accompanies regulatory approval.”). The MDA preempts claims for negligence and failure to warn. See 21 C.F.R. § 808.1(d)(1996); H.R. REP. NO. 853, at 45 (1976) (legislative history). If manufacturers comply with FDA requirements and do not commit fraud, state law claims generally are preempted. See *supra* note 61; see also Lars Noah, *Amplification of Federal Preemption in Medical Device Cases*, 49 FOOD & DRUG L.J. 183, 211 (1994) (“By virtue of the express preemption provision in the MDA, medical devices are unique among products which are subject to regulation by the FDA.”). But see Marianne Lavelle, *Medical Device Makers’ Liability Shield is Dented*, NAT’L L.J., July 8, 1996, at A1 (reporting on Supreme Court holding in *Medtronic, Inc. v. Lohr*, 116 S. Ct. 2240 (1996), that FDA regulation (MDA) does not necessarily preempt consumer suits over faulty medical devices); Marianne Lavelle, *High Court Medical Devices Ruling Muddles Matters*, NAT’L L.J., Sept. 30, 1996, at A9 (reporting that “[c]ourts have split sharply in their readings of a 1996 Supreme Court decision that many had hoped would clear up the issue of when federal regulatory law preempts actions based on state tort and other law”). However, liability for clinical trials is raising. See Michael Traynor, *As Manufacturers Seek Approval for More New Pharmaceuticals, Issue Such as the “Learned*

some companies, such as IVF, are marketing research-stage predictive genetic tests without restraint is a problem of lack of enforcement of existing labeling and other regulations, namely CLIA and professional standards, and not a legitimate basis for introducing even more regulations. Similarly, to the extent that physicians are straying from these protocols, failing to properly counsel their patients, and overusing investigational genetic testing services lacking PPV, they are guilty of practicing poor medicine and should be disciplined professionally.¹⁷¹ Physician malpractice, it may be argued, is not a legitimate basis for imposing more regulations on biotechnology companies. Moreover, to the extent that more regulation is needed, it should come in the form of stronger good-medicine standards imposed on physicians and enforcement of those standards.¹⁷²

The status quo offers some significant public health benefits. First, in addition to developing protocols, industry is addressing ethical issues associated with the commercialization of genetic technologies, and perhaps is doing so more effectively than the government could. Several multinational pharmaceutical companies have financed ethics programs to address these issues.¹⁷³ Similarly, many biotechnology

Intermediary" Rule Will Emerge in Litigation Involving Clinical Trials, NAT'L L.J., Nov. 18, 1996, at B6.

171. "About half of people with a family history of breast or ovarian cancer are likely to request genetic susceptibility (BRCA1) testing when available . . ." *Breast/Ovarian Cancers (Genetics): Many People Prefer Not to Know if They Have Gene Linked to Cancers*, CANCER RES. WKLY, July 15, 1996, available in 1996 WL 2286313 (reporting on study conducted by the Lombardi Cancer Center, Georgetown University, that emphasizes the importance of relaying information about genetic tests themselves to patients). Following the discovery that one percent of Ashkenazi Jewish women carry genetic predisposition to breast and ovarian cancer and despite consumer demand for the test, "almost all leading scientists and two major commercial testing laboratories agreed informally not to offer the test for the mutation to the general public because widespread testing would do more harm than good." Koenig, *supra* note 24, at A23. That consensus was broken, however, by Dr. Joseph D. Schulman, Director of IVF. Dr. Holtzman, Chair of the ELSI Task Force, asserts that Dr. Schulman is "hoodwinking" women by making the IVF test widely available. See Wadman, *supra* note 5, at C3. The National Breast Cancer Coalition and the National Action Plan on Breast Cancer agree that testing should be confined to research settings. See *id.*

172. Consider that the United Kingdom, in comparison with the United States, regulates more experimental medical technology through good medicine standards. See Veronica Henry, *Problems with Pharmaceutical Regulation in the United States*, 14 J. LEGAL MED. 617, 637-38 (1993) ("In Great Britain, investigational and experimental drug use requires certification and licensing; however, therapeutic use, by which physicians administer drugs to their patients, is excluded from the certification requirement.").

173. For example, in the Fall of 1995, SmithKline Beecham (London-based) gave Stanford University \$1 million to start an ethics program in genetics, and the Hastings

companies are hiring ethicists and, at least presumably, taking the advice for which they are paying top dollar.¹⁷⁴

Second, the FDA traditionally has relied heavily on the private medical profession when reviewing new products, and legal liability in the place of FDA involvement (with resulting limitations on liability for compliance) may result in greater quality control.¹⁷⁵ Conflicts associated with the case-by-case nature of the FDA review process, the discretion allotted individual agents, and close ties between members of the medical profession and individual FDA reviewers support proposals to rely upon apolitical advisory committees instead of existing FDA review mechanisms.¹⁷⁶

Center has launched a program called "Values and Biotechnology" with the financial support of Monsanto Co. See Day, *supra* note 31, at A1.

174. Biotech companies are voluntarily and directly addressing ethics issues arising from the commercialization of their technologies. See *id.* Human Genome Sciences, Inc. has hired former opera diva Beverly Sills, who has two children with birth defects and years of service as chairman of the March of Dimes. "All over the biotech industry, companies are hiring ethicists to try to get a jump on these humanistic tangles. Many people in an industry that has the potential to make reality of science fiction are following the rule of look before you leap." *Id.*

175. See, e.g., Claudia MacLachlan, *Spine-Tingling Dispute: Bone Screw Suit Places FDA in 4-Way Squeeze*, NAT'L L.J., Jan. 8, 1996, at A1 ("One of the standard defenses is to wrap your arms and legs around the ankles of some FDA person and say they knew—and a lot of times that is true.") (quoting William W. Vodel, head of FDA practice at Washington D.C.'s Arnold & Porter). Recently, the FDA was pulled into "a four-way crossfire over the way it lets medical devices be used without formal approval. . . . The FDA has also been accused of relying on the advice of doctors allegedly on the take from makers of devices the doctors had tested." *Id.*; see *In re Orthopedic Bone Screw Products Liability Litigation*, 79 F.3d 46 (7th Cir. 1996). This case, which involved the use of screws to affix metal plates to the vertebrae of some 300,000 people despite rejections by the FDA of this use in 1984 and 1985, has highlighted the fact that the FDA cannot always be relied upon as an assurance of quality control. MacLachlan, *supra*, at A1. The problem is that standard of care acceptance may be realized without the FDA. On October 4, 1992, the FDA announced in the Federal Register that it had discovered that the plate and screw devices were in widespread use and considered standard of care by surgical community. At that time, the FDA requested a study by orthopedic professional groups and makers of the spinal implants and, based upon the reported results, the FDA liberalized use. Accusations that the study was corrupt are now the subject of a case brought by plaintiffs against the device's manufacturers. Specifically, attorneys for the plaintiffs in a products liability case over the device later accused the FDA of relying "in part on medical reports from doctors who stood to profit from the device." MacLachlan, *supra*, at A1.

176. See Claire L. Ahem, *Drug Approval in the United States and England: A Question of Medical Safety or Moral Persuasion?—The RU-486 Example*, 17 SUFFOLK TRANSNAT'L. L. REV. 93, 93 (1994) ("Advancements in the pharmaceutical industry have revealed the magnitude of these dissimilarities and the negative effects that result when United States drug officials allow nonscientific considerations to affect their analysis of promising new drugs."); Henry, *supra* note 172, at 637-38, (comparing the U.S. and U.K. systems and concluding that "[t]he British system is more objective and expeditious than the American system. . . . The American system needs to enhance utilization of apolitical

Third, even experimental genetic tests may offer clinical benefits to some patients. These benefits include clarification of risk status, more accurate diagnosis of symptomatic individuals, detection of carrier status, and guidance for selecting the most prudent course of surveillance treatment.¹⁷⁷ For the first time in decades, cancer

advisory committees in the decisionmaking process, much the same way this has been done in the British system.”). *But see generally* ABRAHAM, *supra* note 71, at 246 (“The close institutional relationship between the regulators and the pharmaceutical firms in the U.K. has been associated with a sympathetic view of scientific data from the pharmaceutical industry on the part of the Government scientists and scientific advisers.”). *See also* J. Worth Estes, Book Review, 334 NEW ENG. J. MED. 609, 609 (1996) (reviewing JOHN ABRAHAM, *SCIENCE, POLITICS AND THE PHARMACEUTICAL INDUSTRY: CONTROVERSY AND BIAS IN DRUG REGULATION* (1995)) (“Because the British government wishes to ensure the success of its pharmaceutical industry, its regulatory agencies tend to be protective rather than adversarial, as they are in the United States, where the government is required to be more concerned about protecting patients than about protecting the firms that manufacture medicines.”).

177. *See* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 14 (“A test with a lower sensitivity might have value in certain circumstances, but the organization offering the test must make clear what the limitations are in order to enable providers and consumers to make informed decisions about appropriateness.”); Olufunmilayo I. Olopade, Editorial, *Genetics in Clinical Cancer Care—The Future is Now*, 335 NEW ENG. J. MED. 1455, 1455 (“It is no longer unusual for women with newly diagnosed breast cancer to seek genetic testing before choosing between mastectomy and lumpectomy combined with radiation therapy.”); *see also id.* at 11 (“A direct DNA test can be used to diagnose a genetic disease in symptomatic individuals, predict future disease in healthy people, detect carriers and also for prenatal diagnosis.”); Saltus, *supra* note 134, at 25 (noting that some women already diagnosed with breast cancer perhaps could benefit from testing to make decisions regarding treatment); Wadman, *supra* note 5, at C3 (“They say negative tests have already allowed them to tell women scheduled for preventative breast removal that they don’t need the surgery.”); Weiss, *supra* note 2, at A1 (

For some carefully selected women already diagnosed with breast cancer, a positive test can indicate the need for more aggressive therapy. And for a woman whose mother or sister had breast cancer from a BRCA1 mutation, a negative test can provide some reassurance. What remains unproved, however, is that the test has any value for the more than 95% of women who do not fit into those categories.

). The breast cancer testing issue has caused division among feminist scholars, some of whom feel that impeding the accessibility of genetic tests constitutes paternalism. *See* Wadman, *supra* note 5, at C3 (discussing the availability to Jewish women of a genetic test for breast and ovarian cancer); Weiss, *supra* note 2, at A1. In the words of one woman who was told that she could not have her BRCA1 test results:

Do they really believe that women who test positive are going to immediately race to the nearest operating room to summarily demand the removal of both breasts and ovaries—procedures which, in any event, would require the concurrence of a surgeon? They are underestimating our intelligence to the millionth degree Strangely, men considering surgery for prostate cancer don’t seem to receive this kind of counsel, even though the benefits of surgery haven’t been proven and the operation usually leaves men impotent, incontinent or both.

Wadman, *supra* note 5, at C3.

mortality rates have fallen and, in addition to better treatment, this has been attributed to both prevention and improved diagnosis.¹⁷⁸ Fourth, and perhaps most persuasive, medical science eventually will solve the predictability problem.¹⁷⁹ The present scheme, which generates patient samples and finances research,¹⁸⁰ will most rapidly move genetic medicine to therapeutics and even gene therapies. More regulations could have the exact opposite effect.

B. *Call for Direct Regulation*

Advocates for direct regulation of genetic testing services emphasize that, even though these tests are much more likely to be misinterpreted than traditional diagnostics due to (1) the absence of scientifically valid PPV, (2) the lack of physician understanding about genetics, and (3) the public's interest and faith in genetics enhanced by media coverage, biotech marketing, and information (or misinformation) from providers, these tests are subject to much less regulatory oversight.¹⁸¹ From a mental health perspective, genetic tests for serious diseases may impact patient lives at least as much as traditional diagnostics with established PPV. This is especially true in the absence of reliable studies of the impact of genetic information on patients' lives¹⁸² and the present dearth of trained genetic counselors in practice.¹⁸³ In fact, in the absence of coverage, consumers demanding access to genetic tests may actively avoid genetic counseling due to the

178. See *Breast Cancer Incidence*, *supra* note 134, at 1293-94 (reporting that the overall death rate from cancer fell approximately 3% between 1991 and 1995, and the rate of breast cancer fell 6.3 percent).

179. See Saltus, *supra* note 134, at 25 (arguing that, with time, the tests will be more scientifically reliable and easier to interpret, and that there also will be more health care uses for the information).

180. These research funds are coming out of the pockets of consumers, for most insurance companies will not cover the costs of such experimental health care. See Boyle, *supra* note 13, *supp.* at S5 ("While exact data on private insurance coverage are scarce, most genetic services—preventive, screening, and counseling—are not covered because the interventions are considered either 'investigational' or 'not medically necessary.'").

181. See *generally supra* Parts II.B & C.

182. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 33 ("People at risk of disease in high risk families may have built up a complex mechanism to deal with the perception that they are affected... Genetic counseling can be extremely time-consuming."). However, Kaiser Permanente currently is developing a clinical practice guideline for BRCA1 testing and introducing a confidential patient registry to ensure long-term follow up. See *BRCA1: Are You Ready for Clinical Testing?*, PERSP. GENETIC COUNSELING, Summer 1996, at 12.

183. See Malinowski, *supra* note 125, at 351-52 & n.104.

costs it adds.¹⁸⁴ Over-reliance on negative test results¹⁸⁵ and over-treatment based upon positive test results¹⁸⁶ are strong possibilities, if not probabilities. Also, in the absence of adequate consumer safeguards to ensure genetic privacy and counseling and awareness of these dangers *before* the decision to undergo genetic testing is made, those who subject themselves to genetic testing may find that they also are subjected to discrimination from employers and insurers.¹⁸⁷ In addition, family members may be subject to discrimination based upon the results of genetic testing they did not even undergo.¹⁸⁸

Advocates for direct regulation also argue that OncorMed's prudence in developing a thorough protocol cannot be relied upon as established industry practice. Rather than being representative of long-term industry behavior, these precautions may be a reflection of the fact that OncorMed is the first biotechnology company to make predictive genetic testing available outside the major research centers and, as such, it has been painstakingly careful. Similarly, the influence that drug developers and manufacturers exercise over scientific research must not be underestimated. Industry influence is not only

184. Many new predictive genetic tests are investigational and, therefore, often are paid for out of consumers' pockets. See BLATT, *supra* note 21 ("While genetic counseling is necessary to make informed decisions about clinical genetic tests, as a sole service, it is often not covered by insurance."). Accordingly, it is unlikely that consumers are going to seek out counseling due to the added cost. See Malinowski, *supra* note 125, at 351 & n.106; see also *First BRCA1 Test Hits the Market*, *supra* note 65, at 3 ("While it may be difficult to find two people who agree on all aspects of what is to be done, virtually all the opponents of immediate commercialization of genetic testing agree that counseling patients before and after they are tested is anything but a straightforward matter.").

185. See Wadman, *supra* note 5, at C3 ("Scientists argue that testing in nonresearch settings is fraught with peril. Negative test results, they say, could lull women into a false sense of security, when in truth 90 to 95 percent of breast and ovarian cancers aren't inherited but occur spontaneously.").

186. The investment in technology to identify breast cancer has not been accompanied by similar investment to understand its growth and spread. See Plotkin, *supra* note 134, at 54-55. The failure to appreciate cell growth differences in breast cancer, coupled with mammography, may have resulted in over-diagnosis and treatment—including unnecessary mastectomies. See *id.* at 70. The end result is that breast cancer is twice as likely to be diagnosed today as it was 60 years ago, but mammography studies show no overall difference in mortality from breast cancer between treatment and control groups. See *id.* at 69 (citing Swedish, Irish, and Canadian studies). Widespread BRCA testing could greatly exacerbate this problem.

187. See generally *supra* note 58. See also Barash & Alper, *supra* note 58, at 43; Geller, *supra* note 58, at 71.

188. See Act Concerning Genetic Testing and Privacy and Medical Underwriting, N.J. S.B. 695 & 854, at § 2.d (1996) ("An analysis of an individual's DNA provides information not only about an individual, but also about the individual's parents, siblings and children, thereby impacting family privacy, including reproductive decisions.").

impacting the course of science,¹⁸⁹ but is tainting the safeguard of scientific peer review.¹⁹⁰ In this modern age of privatized R&D, academic institutions and their individual researchers are highly susceptible to the influence of the biotechnology industry and may even hold royalty interests in the industry's products.¹⁹¹ Accordingly,

189. There is fear in the United States that creativity and objectivity in basic science is being lost due to the privatization of R&D. Rather than allowing researcher discretion and the raising of a general floor in science, basic science is being directed by corporate decisions to pursue and develop research discoveries solely according to their commercial viability. See, e.g., ABRAHAM, *supra* note 71, at 245 ("Since the career structure of academic medics rewards them for publications, there is an institutional incentive for such medics to work co-operatively with an industry that can provide the funding for publishable research."); Christine Gorman, *Has Gene Therapy Stalled?*, TIME, Oct. 9, 1995, at 62, 62-63 (noting that, while gene therapy holds extraordinary promise, enthusiasm and financial pressures may have caused a premature push to market that is sacrificing basic science and human safety for a quick return on investment). See also Malinowski & O'Rourke, *supra* note 20, at 187 (discussing the concern that the alliance nature of the biotech industry may be skewing the course of basic science). This concern has been substantiated in part by a study published in the New England Journal of Medicine based upon data collected from 2,052 faculty members from October 1994 to April 1995. According to the study, "faculty members receiving more than two thirds of their research support from industry were less academically productive than those receiving a lower level of industrial support" and "faculty members who have research relationships with industry are more likely to restrict their communication with colleagues." David Blumenthal et al., *Participation of Life-Science Faculty in Research Relationships with Industry*, 335 NEW ENG. J. MED. 1734, 1734 (1996).

190. See Ralph T. King, Jr., *Bitter Pill: How a Drug Firm Paid For University Study, Then Undermined It*, WALL ST. J., Apr. 25, 1996, at A1. There is anecdotal evidence that industry is tampering with scientific integrity. The "Synthroid affair" exemplifies the danger of industry-financed research. A manufacturer paid \$250,000 to finance research to establish that cheaper drugs were not as effective as its product. When the researcher attempted to publish findings of bioequivalency between the drug and other, much cheaper drugs, the manufacturer worked aggressively to discredit the research. See *id.* ("The Synthroid affair illustrates what some leading scientists decry as increasingly frequent corporate attacks on open scientific debate, at a time when industry-supported research is crucial because of a shrinking government role in medical research."). Similarly, "[i]n a recent article in the New England Journal of Medicine, Steven A. Rosenberg, chief surgeon of National Cancer Institute, cited what he said were four instances of promising research being squelched or slowed by corporate sponsors' demands for secrecy to preserve possible competitive advantage." *Id.*

191. See David Blumenthal et al., *Relationships Between Academic Institutions and Industry in the Life Sciences—An Industry Survey*, 334 NEW ENG. J. MED. 368, 368 (1996) ("Ninety percent of companies conducting life-science research in the United States had relationships involving the life sciences with an academic institution in 1994. Fifty-nine percent supported research in such institutions, providing an estimated \$1.5 billion, or approximately 11.7 percent of all research-and-development funding received that year."); see also Steven A. Rosenberg, *Secrecy in Medical Research*, 334 NEW ENG. J. MED. 392, 392-93 (1996) (

The conduct of medical research is in increasing jeopardy. . . . Secrecy about methods and results has become a common and accepted practice. . . .

the influence of the biotechnology industry over public health policy must be checked, not augmented by a *carte blanche* federal regulatory approach.

C. Drawing Conclusions

The present regulatory scheme for commercialization of predictive genetic testing services consists essentially of reliance on market forces, legal liability, and the judgment of primary care physicians. Through access to patient samples and the opportunity to capture the costs of research, this approach is financing and advancing biotechnology research. Innovative therapeutics and gene therapies for life-threatening and widespread diseases such as breast cancer are becoming vivid possibilities.

Nevertheless, the research-stage nature of predictive genetic tests, such as the existing tests for BRCA mutations, and resulting uncertainties make these tests currently unacceptable for broad commercialization.¹⁹² Legal liability places the burden of quality assurance on health care consumers who are the people that need to be protected,¹⁹³ and the transaction costs of shaping public health policy through litigation can be immense. Indeed, several cancer organizations and Jewish community groups have drafted position statements opposed to the commercialization of predictive breast cancer testing given the lack of safeguards to ensure oversight and

The increasing involvement of for-profit biotechnology companies in medical research has provided new sources of funding, but with this involvement has come an emphasis on the ethical and operational rules of business rather than on those of science.

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192. See Mark et al., *supra* note 133, at 405 ("Predictive testing should be considered investigational, and testing for purposes other than health care should be discouraged."). Despite the truth of the statement, it has become almost cliché in circles of genetic experts to say that we should have learned from the sickle cell experience in the early 1970s in which a screening program caused widespread anxiety and many breaches of confidentiality. See Brom, *supra* note 27, at 129; *supra* note 126.

193. Law should be used to prevent predictable problems and minimize the harm. See Annas, *supra* note 14, at 22 (rejecting *laissez-faire* strategy to let the market determine which genetic tests are done on the grounds that law should be used to prevent problems and "lawsuits for breaches of privacy have not often been pursued (because the private information is usually made known to even more people in the process)"). As observed by Professor Paul Starr, "[t]he very circumstances of sickness promote acceptance of [physicians'] judgment." PAUL STARR, *THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE* 5 (1982).

accuracy, informed consent, and confidentiality.¹⁹⁴ Regulatory safeguards are needed to ensure that predictive genetic technology, which offers much promise, does not detract from public health because it is applied in a shortsighted, irresponsible fashion. Regardless of the failures and shortcomings of FDA regulation of traditional diagnostics, medical and public health officials must directly address the issue of quality assurance for predictive genetic testing services. They must introduce and enforce consumer safeguards tailored to this innovative technology.

V. PROPOSALS FOR CHANGE

Public health education developed with consumer input must be included in any strategy to regulate the commercialization of genetic testing services.¹⁹⁵ Nevertheless, a broader strategy is needed. Before sorting through the numerous options,¹⁹⁶ medical and public health officials must determine which approach or combination of approaches is likely to prove most effective. A fundamental point of differentiation is between protecting consumers (1) through added market review and approval restraints that more carefully monitor market access to health care consumers or (2) through the health care profession as a matter of good-medicine standards. In other words, the two fundamental regulatory approaches (which may be used conjunctively) are (1) to introduce restraints to keep health care

194. See, e.g., AMERICAN CANCER SOCIETY, MASSACHUSETTS DIVISION, *GENETIC TESTING: PATIENT PRIVACY AND DISCRIMINATION CONSIDERATIONS* (1995); DRAFT STATEMENT, THE JEWISH WOMEN'S COALITION ON BREAST CANCER (1996) ("The recent identification of a genetic variation that may predict breast cancer is provoking immense anxiety and obscuring vital information."); DRAFT STATEMENT, HADASSAH, *BRCA1 GENE, GENETIC TESTING AND INSURANCE DISCRIMINATION* (1996) ("Hadassah is . . . concerned that this new genetic information or individual's requests for genetic counseling services may result in higher health insurance premiums, changes in terms or conditions, or outright denial or cancellation of coverage."); MASSACHUSETTS BREAST CANCER COALITION, *WHAT YOU NEED TO KNOW BEFORE CONSIDERING GENETIC TESTING FOR HERITABLE BREAST CANCER 1-2* (1996) (identifying the following considerations: (1) the potential advantage of the test to an individual is limited, (2) there is no known effective prevention for breast cancer, (3) a positive test result does not mean that you will get breast cancer, (4) a negative test result does not mean that you will not get breast cancer, and (5) getting tested may carry psychological, social, financial, and legal ramifications).

195. See generally BLATT, *supra* note 21.

196. The mechanism for regulation recognized by the ELSI Task Force includes: (1) adoption of industry-wide codes or policy statements; (2) recommendations from professional societies; (3) extension of existing state or federal regulations to cover unique areas of genetic testing; and (4) new legislation. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 37.

products that unduly endanger consumers off of the market or (2) a “good medicine” regulatory approach that uses professional self-regulation (peer review and norms) and legal liability. The principles and recommendations proposed by the National Task Force combine these approaches, with an emphasis on the good medicine approach:

TABLE I
HIGHLIGHTS: PROPOSED RECOMMENDATIONS OF THE TASK FORCE ON
GENETIC TESTING¹⁹⁷

<i>KEY PRINCIPLES</i>	
<i>VALIDITY AND UTILITY OF GENETIC TESTS</i>	<p>As a prerequisite for acceptance in clinical practice, data sufficient to demonstrate clinical benefits and risks from both positive and negative results must be collected.</p> <p>An IRB must approve the protocols used for genetic tests.¹⁹⁸</p>
<i>LABORATORY QUALITY AND CERTIFICATION</i>	<p>Despite the CLIA certification requirement imposed on most clinical laboratories, "current regulations do not adequately ensure the quality of genetic testing."¹⁹⁹</p>
<i>PROFESSIONAL COMPETENCE IN GENETICS</i>	<p>"Health care professionals involved in the provision of genetic tests should be well-informed about their implications, benefits and risks."²⁰⁰</p> <p>"[N]ot all providers in practice today may have adequate competence to offer and interpret genetic tests."²⁰¹</p>
<i>RARE GENETIC DISEASES</i>	<p>"At a time when genetic tests for common complex disorders are increasing, tests for rare disorders may be developed at a slower rate than in the past."²⁰²</p>
<i>INFORMED CONSENT AND CONFIDENTIALITY</i>	<p>"Informed consent for a validation study must be obtained whenever the specimen can be linked to the subject from whom it came."²⁰³</p> <p>"The responsibility for providing information to the individual lies with the referring provider, not with the laboratory performing the test."²⁰⁴</p>

197. This summary is based upon Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4539-47 (1997).

198. *See id.* at 4540.

199. *Id.*

200. *Id.*

201. *Id.*

202. *Id.*

203. *Id.*

204. *Id.*

	<p>“Respect for personal autonomy is paramount. People being offered testing must understand that testing is voluntary.”²⁰⁵</p> <p>“Results should be released only to those individuals to whom the test recipient has consented or subsequently requested in writing.”²⁰⁶</p> <p>“Health care providers have an obligation to the person being tested not to inform other family members without the permission of the person tested except in extreme circumstances.”²⁰⁷</p>
<i>RECOMMENDATIONS</i>	
<i>A GENETICS ADVISORY COMMITTEE</i>	<p>The Secretary of HHS should create a federally chartered Advisory Committee on Genetics and Public Policy (“Advisory Committee”) whose members should include stakeholders in genetic testing.²⁰⁸</p> <p>The Secretary also should utilize an interagency group to assist the Advisory Committee and develop coordinated and consistent genetic testing policies.²⁰⁹</p>
<i>NEED FOR INTERIM ACTION</i>	<p>The Secretary of HHS should “use existing agencies and policies to ensure that the public will have adequate protection from predictive genetic tests that have not been adequately validated and whose clinical utility has not been established.”²¹⁰</p> <p>To accomplish this, the Secretary may either (1) use its authority under the MDA or (2) reimburse under Medicaid and Medicare only when genetic tests are performed in laboratories that can establish that the test has been clinically validated and that they are qualified to perform them.²¹¹</p>

205. *Id.*

206. *Id.* at 4541.

207. *Id.*

208. *See id.*

209. *See id.*

210. *Id.*

211. *See id.*

*ASSURING THE
VALIDITY AND
UTILITY OF NEW
GENETIC TESTS*

A National Genetics Board (NGB) should be created “to assure the protection of human subjects in the development of genetic tests with the potential to predict future disease.”²¹²

“NGB would develop a checklist that would enable local IRBs to identify protocols that meet criteria for stringent scrutiny.”²¹³

The FDA should establish a Genetics Advisory Panel under the MDA that requires new genetic tests to meet criteria for stringent scrutiny.²¹⁴

CDC, in cooperation with NCHGR, should expand monitoring of genetic disorders to provide data on the validity of tests and post-test interventions and establish procedures for tracking those who undergo genetic testing.²¹⁵

The FDA should grant conditional premarket approval for genetic tests with the potential to make significant public health contributions and place the burden on developers to collect data and make it available to the FDA.²¹⁶

NGB should serve as a clearinghouse for technology assessments and make recommendations on appropriate use of genetic tests.²¹⁷

*ASSURING
LABORATORY
QUALITY*

A national accreditation program of quality assurance and proficiency testing for genetic tests equivalent to or more stringent than those of New York State and the College of American Pathologists/American College of Medical Genetics (CAP/ACMG), should be established under CLIA. The accreditation program should include proficiency testing and inspection of laboratories that perform genetic tests.²¹⁸

212. *Id.* at 4544.

213. *Id.*

214. *See id.* at 4544-45.

215. *See id.* at 4545.

216. *See id.*

217. *See id.*

218. *See id.*

Until a national accreditation program is established under CLIA, the CAP/ACMG Molecular Pathology program, expanded to encompass all genetic testing methods currently in use, should be implemented as a national program.²¹⁹

A Genetic Advisory Committee to CLIA should be established to help address the deficiencies of CLIA. The work of this committee should be coordinated with other HCFA programs and the work of FDA, CDC, and other federal agencies involved in establishing policies for genetic testing.²²⁰

CAP/ACMG should seek input from consumer groups such as the Alliance of Genetic Support Groups and National Society of Genetic Counselors (NSGC) when setting standards.²²¹

CAP/ACMG should periodically publish and make public a list of laboratories performing genetic tests in compliance with its voluntary program.²²²

“Managed care organizations and other third-party payers should limit reimbursement for genetic tests to the laboratories on the published list”²²³

“[E]fforts should be made to harmonize international laboratory standards to assure the highest possible laboratory quality for genetic tests.”²²⁴

*PROVIDER
COMPETENCE*

“The Task Force endorses the recent establishment of a National Coalition for Health Professional Education in Genetics by the American Medical Association, the American Nurses Association, and the NCHGR.”²²⁵

A core curriculum in genetics should be developed.²²⁶

219. *See id.*

220. *See id.*

221. *See id.* at 4545-46.

222. *See id.* at 4546.

223. *Id.*

224. *Id.*

225. *Id.*

226. *See id.*

Certification and other credentialing mechanisms should be used to promote competency.²²⁷

“Predictive genetic tests requiring stringent scrutiny, as previously described, should be among those for which special credentials are needed.”²²⁸

Primary care providers and other nongeneticist specialists should be involved in genetic testing but only after gaining sufficient training and knowledge.²²⁹

Credentialing bodies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the National Committee for Quality Assurance (NCQA) should be utilized.²³⁰

“Except when time is of the essence, such as with certain prenatal genetic tests, obtaining informed consent and actually performing the test should be delayed several days after the test is offered and information given to the patient.”²³¹

*RARE GENETIC
DISEASES*

“The quality of laboratories providing tests for rare diseases must be assured, and a comprehensive system to collect data on rare diseases must be established.”²³²

“The Task Force recommends that NIH give [the NIH Office of Rare Diseases (ORD)] a mandate to coordinate . . . public and private efforts to improve awareness of rare genetic diseases.”²³³

“ORD should identify laboratories world-wide that perform tests for rare genetic diseases, the methodology employed, and whether the tests they provide are in the investigational stage, or are being used for clinical diagnosis and decision making.”²³⁴

227. *See id.*

228. *Id.*

229. *See id.*

230. *See id.*

231. *Id.* at 4546-47.

232. *Id.* at 4547.

233. *Id.*

234. *Id.*

“ORD should also be responsible for assuring that tests for rare genetic diseases, which have been demonstrated to be safe and effective, continue to be available”²³⁵

“[A]ny laboratory performing any genetic test on which clinical diagnostic and/or management decisions are made should be certified under CLIA.”²³⁶

“Directories of laboratories providing tests for rare diseases should indicate whether or not the laboratory is CLIA-certified and whether it has satisfied other quality assessments, such as the CAP/ACMG program.”²³⁷

In an era of deregulation, and in light of the deficiencies of CLIA and a general failure to enforce CLIA regulations with any consistency, the good-medicine approach to protecting consumers should be given careful consideration.²³⁸ This provider-centered approach could prove highly effective for physicians to control consumer access to predictive genetic testing services. Their involvement is absolute, meaning that consumers cannot have predictive genetic tests run on their samples without a primary care physician “middleman” making the procedure available. Lack of physician knowledge about the predictive services they are discussing with and making available to their patients, and the resulting lack of appreciation for the limitations of the technology and its impact on patients’ lives, is simply inexcusable. Under no circumstances should physicians be making health care technology available unless they fully understand that technology. Patients, too, must be given information regarding the nature of investigative testing. Appropriate pretest counseling must be mandated.

The willingness of physicians to stray from such basic responsibilities may reflect the fact that many consumers are paying for investigational genetic testing services out of their pockets (due to both the refusal of insurers to cover experimental services and

235. *Id.*

236. *Id.*

237. *Id.*

238. See Meeting Minutes, *supra* note 1, at 7 (stating that one member “expressed the view that CLIA is ill-equipped for overseeing PT for genetics labs, and suggested that in this era of de-regulation, professional genetics organizations may be better suited to the task”); see also Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4545 (1997) (discussing the insufficiencies of CLIA).

consumer fears of genetic discrimination). Under this payment arrangement, physicians do not have to account to insurers and managed-care administrators for the costs of genetic testing services. Although consumer demand for access to predictive genetic testing services may become (or already may be) significant, medical and public health officials cannot accept consumer demand as an excuse for the practice of substandard medicine.²³⁹ Acceptance of such an excuse would carry tremendous ramifications,²⁴⁰ especially in an age of managed care when physician compensation is tied to the number of patients a physician maintains. Other potential conflicts of interest are equally troubling.²⁴¹ Similarly, the physician-patient relationship does not allow the benefits from advancements in research, regardless of how profound they may be, to serve as an acceptable rationale for the practice of irresponsible medicine.²⁴²

Implementation of the laboratory quality assurance recommendations of the ELSI Task Force (meaning a CLIA laboratory accreditation program modeled after the CAP/ACMG Molecular

239. Consumers cannot be entirely relied upon to assess their health care needs and the quality of the care they receive. *See generally* Jason Ross Penzer, Note, *Grading the Report Card: Lessons from Cognitive Psychology, Marketing, and the Law of Information Disclosure for Quality Assessment in Health Care Reform*, 12 YALE J. ON REG. 207 (1995) (discussing the limitations of consumer-directed information disclosure proposals as a quality assurance system). *See, e.g.*, David L. Kaserman, *Reimbursement Rates and Quality Care in the Dialysis Industry: A Policy Discussion*, 8 ISSUES LAW & MED. 81, 82 (1992) (noting that consumers tend to be more satisfied with shorter dialysis running times, even though reducing running times correlates with increased incidents of hospitalization and mortality).

240. *See generally* Malinowski, *supra* note 125 (noting that managed care affects the physician's relationship with the patient in that a large amount of discretion in decisionmaking belongs to the health care provider).

241. *See* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 34 (Principle III-17 states in part that

Any actual or potential conflict of interest should be disclosed to persons being offered genetic testing. . . . One situation arises when the referring health care provider, or a provider/investigator who has developed a test, has a financial stake in a clinical laboratory. Another situation arises when those counseling people about testing are remunerated from funds generated by performance of the test itself and not entirely from their counseling activities.

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242. *See generally* David Orentlicher, *Health Care Reform and the Patient-Physician Relationship*, 5 HEALTH MATRIX 141 (1995) (discussing concerns that health care reform would impinge on patient-physician relationship). The paradox between advancing medical science to benefit all children at the sacrifice of individual children who are the subjects of research is addressed in Mclean, *supra* note 19, at 114 ("The paradox then may be that in order to protect some children, we need to use other children as subjects of research to gain the knowledge necessary for prevention and therapy.").

Pathology Program) to ensure sequencing proficiency must be accompanied by comprehensive genetic medicine measures. Medical and public health officials must introduce and enforce good medicine guidelines that are carefully tailored to directly address predictive genetic testing services.²⁴³ For example, federal regulators should consider imposing a mandatory minimum PPV standard for genetic testing services performed outside of major academic research centers when results are made available to those who undergo the testing. Moreover, written proof of compliance—a written showing of PPV—should be a prerequisite for charging to recover costs. Similarly, providers should be required to establish competence in genetics as a prerequisite for reimbursement for the genetic testing services they provide.²⁴⁴

243. The need to have regulations tailored specifically to genetics has been recognized by many, including Dr. Holtzman, Chair of the ELSI Task Force:

“Genetic tests have many distinct, unique problems that cry out for a separate regulatory category,” noted Holtzman. For example, tests used for predictive purposes are not used primarily in sick people, as are most other diagnostic tests, but rather to predict future disease. Moreover, physicians often have little in the way of clear-cut interventions to offer when a test reveals that a patient is predisposed to develop a gene-related disorder. Predictive genetic tests also may involve issues of prenatal testing and termination of pregnancy, and they have implications not only for the individual being tested but for family members as well.

Stephenson, *supra* note 15, at 1662. In the area of FDA reform, industry is *requesting* this same level of detail. *See* Fox, *supra* note 82, at 698; *see also* Translating Advances in Human Genetics into Public Health Action (undated) (background document prepared for a meeting to discuss genetics in public health at the Center for Disease Control and Prevention on January 27-28, 1997) (on file with authors). An Ad hoc Task Force on Genetics in Disease Prevention was appointed by the CDC Director in September of 1996 to (1) develop a strategic plan for CDC-wide genetics programs; (2) coordinate and support program efforts involving multiple centers, institutes, and offices at the CDC; and (3) convene constituents and consultants to obtain input on strategic planning and priorities for CDC activities related to genetics in public health. The stated mission is to “integrate knowledge of human genetics into effective and ethical public health actions that promote health and prevent disease and disability. CDC, in collaboration with its partners, will accomplish this mission by assessing the public health impact of human genetic variation and its interaction with modifiable risk factors; developing a sound framework of public health policies, recommendations, and guidelines for the use of genetic tests and services; developing and evaluating population-based prevention programs that include genetic tests and services in the prevention of disease and disability; and disseminating genetics information and providing public education and professional training.” *Id.*

244. This proposal has received support from members of the ELSI Task Force. *See* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 25. Because the field is evolving and advancing so rapidly, even after making such a showing, physicians should be subjected to continuing education requirements in genetic medicine. *See id.* at 23-24 (“Principle III-2: Some documentation of continuing education in the area of human and medical genetics should be required for physicians offering genetic tests, including primary care providers.”);

Such standards must be introduced nationally to avoid an industry “race to the bottom” at the state level. Specifically, a failure to introduce national standards is likely to instill the wrong public-health incentives by rewarding states that adopt a *laissez-faire* approach to attract industry. Standards also must be explicit enough to be enforceable. One of the advantages of express quality standards or codes of practice is that they will remove the amorphous standard of care (“the rest of the profession is doing it”) defense to liability.²⁴⁵ With more specific standards in place, physicians will be liable for not adhering to these standards, regardless of what the rest of the profession is doing.

There is ample support within the medical profession for such standards, most notably from Francis Collins, head of the HGP.²⁴⁶ Ironically, many medical professionals vocally oppose making BRCA

see also Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4546 (1997) (proposing the development of a satisfactory curricula and examination and recertification programs).

245. The United States is like the United Kingdom in that, absent specific codes of practice, the test for liability remains effectively a professional one:

The test . . . effectively states that a doctor will not be negligent if she acts in accordance with a practice held to be reasonable by a responsible body of medical opinion. Therefore, it could be said, although somewhat simplistically, that as long as some doctors are behaving in a certain way, then no liability will attach. . . .

This makes it likely that a responsible body of medical opinion will be found to endorse whatever the individual doctor has or has not done, thereby virtually ensuring that legal liability will not be attributed. However, it should be said that there is an increasing trend in contemporary medicine to develop codes of practice that might be thought of as codes of best practice. If such codes are developed in relation to genetic screening, it will become harder to argue in favor of the doctor who deviates from that code

Mclean, *supra* note 19, at 126-27.

246. *See* ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 15 (“Professional societies, such as the American College of Medical Genetics, the American Society of Human Genetics, and the Council of Regional Networks for genetic Services have published statements regarding appropriate and inappropriate use of specific tests.”); Collins, *supra* note 2, at 188 (“[I]t is critical that we create safeguards to ensure that the benefits of testing exceed the risks.”); *see also* Saltus, *supra* note 134 (“Dr. Francis Collins, the head of the National Center for Human Genome Research, wrote in a medical journal last January that he was concerned about commercial motives spreading the test outside research programs. Last week he said he still believes testing should be under a research umbrella ‘until such time as we have better answers’ about its usefulness.”); Weiss, *supra* note 2 (“[S]everal prestigious scientific organizations—including the American Society for Human Genetics, the National Advisory Council for Human Genome Research and the National Action Plan on Breast Cancer, which is coordinated by the U.S. Public Health Service—have come out against commercialization of the BRCA1 test, the first crude predictor of cancer risk to come on the market.”).

testing available to consumers outside the major research centers, even though the medical profession shares responsibility for this occurrence by failing to effectively self-regulate.²⁴⁷ Moreover, generating tailored standards at a national level with professional and consumer input has been made more possible through recent advances in communication. In fact, in an age of global communication, it also is possible to review, and perhaps adopt, modified versions of health care quality standards from abroad for innovative technologies that have been proven effective in practice.²⁴⁸ One possibility is the U.K.'s standards (and underlying research) regarding genetic diagnosis for late-onset disorders in children.²⁴⁹

Still, thoughtful standards alone may not be enough to counter the pressures on providers from consumers, behind-the-scene managed care administrators who want to keep consumers enrolled while minimizing costs, and industry. Therefore, to make the genetic-test quality standards imposed on practicing physicians enforceable, the introduction of codified professional standards must be accompanied by regulatory restrictions on predictive genetic testing.²⁵⁰ In light of

247. See Saltus, *supra* note 134, at 25; Weiss, *supra* note 2, at A1.

248. See Malinowski, *supra* note 29, at 122.

249. Professor George Annas is attempting to organize a Global Physicians and Lawyers for Human Rights Network to introduce enforceable international standards for medical technology such as genetic testing. See Vicki Brower, *Lawyers, Physicians Seek Genomics Rules*, 15 NATURE BIOTECHNOLOGY 10 (1997). The International Bar Association, the world's largest legal organization for lawyers, supports a treaty proposed to set minimum standards for the use of genetic information. See *id.* This treaty was released November 1996 in Berlin, Germany. See *id.*; see also Mindy H. Chapman, Comment, *RX: Just What the Doctor Ordered: International Standards for Medical Devices*, 14 Nw. J. INT'L. & BUS. 566 (1994).

250. See Weiss, *supra* note 2, at A1 (

At the [ELSI Task Force] meeting last month, representatives of the biotechnology industry said it is the doctor's job to make sure that patients understand the risks and benefits of being tested. Doctors said they were still getting up to speed in genetics and would be unable to stem the tide of patient demand if testing were not subject to regulatory restrictions. And insurers said they would go out of business if they were restricted from having access to genetic information.

); *FDA Needs to Regulate*, *supra* note 63, at 1627 (

The US Food and Drug Administration (FDA, Rockville, MD) needs to muster the political will to take up the regulation of genetic testing, not just of diagnostics manufactured as kits, but also of the in-house protocols ("home brews") that constitute most susceptibility tests.

Although the US Health-Care Financing Administration does have some oversight (under the Clinical Laboratory Improvement Amendment of 1988), as do institutional review boards at various institutions, the oversight provided varies widely and does not inspire confidence in the end results.

the public and political pressures on the FDA, such regulation might best be introduced through the CDC, FTC, HCFA, or HHS by, for example, modifying CLIA. To minimize duplication of regulatory efforts, there must be horizontal regulatory coordination at the federal level and vertical coordination between federal and state efforts. This coordination cannot be accomplished without the establishment of a federal body with the sole responsibility of achieving this objective and the political independence and authority to do so.

One logical option is to introduce complementary criteria on research laboratories (meaning any laboratory performing predictive genetic testing) regardless of whether the testing they perform is offered as research, investigational, or off-label. Like physicians, research laboratories control access to predictive genetic testing services, in that their involvement also is absolute. Accordingly, careful consideration should also be given to the laboratory-quality principles developed by the ELSI Task Force, which are attached in part as Appendix II, and the more recent Proposed Recommendations summarized in Table I. Another option is to introduce uniform proficiency testing (PT).²⁵¹ As suggested by the ELSI Task Force, such a requirement could be enforced by making it a precondition for reimbursement for testing services.²⁵² In its more recent recommendations, the Task Force has proposed introducing a registry of laboratories in compliance with national standards, coupled with limiting reimbursement by third-party payers to tests performed by

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251. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 7 (“There was a general consensus among Task Force members that, be it mandatory or voluntary, a uniform national genetics PT program would be preferable to the assortment of approaches used today.”). Some members of the ELSI Task Force have suggested that:

[W]hile CLIA does not require PT [proficiency testing] for genetic testing, genetic labs would be subject to CLIA’s quality assurance (QA) requirements. Under QA inspection, laboratory surveyors could ask for evidence of quality testing, and may obtain the results of voluntary PT by the lab. (Labs cannot conceal poor PT results from surveyors.) If the voluntary PT results showed the lab was deficient, HCFA could take appropriate measures under CLIA to make sure the lab improves. Such measures could include a plan of correction, on-site monitoring, “cease and desist” orders, or perhaps even court action. Lebovic emphasized that mandatory PT under CLIA is intended as more of an educational tool than a punitive device. Still, revising CLIA to require that genetics labs undertake PT would help insure the quality of their testing.

Meeting Minutes, *supra* note 1, at 6-7.

252. See Meeting Minutes, *supra* note 1, at 7.

laboratories on the list.²⁵³ Regardless of what medical-science, quality-assurance safeguards are introduced on the federal level, there must be recognition of the fact that genetic science is constantly and rapidly evolving. Accordingly, all review must be ongoing.²⁵⁴

Federal standards also must be introduced to ensure that the IRB mechanism carries legitimacy.²⁵⁵ At the very least, the CLIA provisions calling for the use of IRBs and giving them authority must be expanded to address their composition and to establish standards for approval of any human research, federally funded or not. In light of the authority IRBs carry and because they are the primary mechanism assuming the sufficiency of the scientific process and protecting the rights of participating subjects, there must be prescribed elements for structuring IRBs that promote impartiality and the enforcement of good-medicine standards. The discretion allowed institutions when constructing IRBs must be curtailed.²⁵⁶ Strict

253. See Proposed Recommendations of the Task Force Genetic Testing, Meeting Notice, 62 Fed. Reg. 4539, 4546 (Nat'l Insts. Health 1997).

254. See ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 36 (

Principle IV-1: All elements of the genetic testing process need ongoing review and oversight. Ongoing review of the genetic testing process is needed to ensure the integrity of testing programs and to avoid potential abuses. . . . An expanded role of institutional review boards, the recognition of genetics as a discrete entity by CLIA administrators and FDA, and the creation of a special national body with authority to review genetic testing are some options, which are not mutually exclusive, currently under consideration.

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What patients should be told about a test and its results may change considerably due to the research nature of the testing and ongoing data collection and compilation. This is the cost of making service available before thorough clinical study and under tight restrictions.

255. The incredible lack of such standards is summarized in Palca, *supra* note 70, at 4

(

Since federal agencies clearly aren't prepared to oversee research themselves, they usually turn to IRBs to do the job. . . . In some cases, the board's workload is such that it spends only one or two minutes on each study under review, and for most IRBs that workload will increase. . . .

. . . Collegial ties among IRB members and researchers whose work they were being asked to review could hamper an IRB member's ability to critically evaluate protocols.

). See also Proposed Recommendations of the Task Force on Genetic Testing, Meeting Notice, 62 Fed. Reg. at 4544 ("The Task Force is concerned that the high workload of IRBs, their variability in community representation, in evaluating protocols, and in expertise germane to the review of genetic tests, as well as the conflicts of interest that can arise in local review, impairs current review of genetic tests that warrant stringent scrutiny.").

256. As recognized by some members of the ELSI Task Force, entities constructing IRBs have significant discretion:

[T]he subject of IRBs is rife with questions. Who should sponsor IRBs? Who should sit on IRBs? Are all IRBs equipped to oversee investigational use of

conflict-of-interest and disclosure requirements are needed, including requirements that any compensation for participation in IRBs be reported and disclosed publicly. Also, the composition of IRBs should be regulated to the extent necessary to ensure rigorous, intellectually honest, and scientifically valid review. The importance of such regulation is made especially acute by the proposed disbanding of the Recombinant DNA Advisory Committee (RAC), "a venerable panel of scientists, ethicists and other experts at the National Institutes of Health that for two decades has shined the spotlight of public accountability on the genetics revolution."²⁵⁷ The peer review nature of IRBs suggests that the traditional research/clinical division in medicine should be bridged for IRB standards by collaboration between professional organizations that focus on both research and

genetic tests? Should more than one IRB be used? Are there conflict-of-interest problems with IRBs established by entities with a financial stake in the products being reviewed?

... Dr. Murphy of OncorMed explained that her company has created an IRB group, and has no interaction with the IRB other than for review of OncorMed's protocols. ... The IRB qualifies under both Health & Human Services and FDA IRB regulations, and its members include two pathologists, a bioethicist, a nurse, a consumer and a lawyer plus a variety of ad hoc experts who rotate for different protocols.

Meeting Minutes, *supra* note 1, at 4-5. See generally ABRAHAM, *supra* note 71 (reporting a lack of impartiality between science community representatives on IRBs and researchers responsible for the science at issue, as there is a revolving door and often professional and financial entanglements between those two groups).

257. Rick Weiss, *It Maybe Over for Biotech Oversight Panel*, WASH. POST, May 29, 1996, at A17 ("The Recombinant DNA Advisory Committee [RAC] ... is poised to get its plug pulled."). Despite its accomplishments, which include (1) the first guidelines for scientists wishing to create genetically engineered microbes; (2) the first formal review system for proposals to insert new genes into people; and (3) the first approval of a human gene therapy experiment, RAC faces a proposal in the federal register by NIH Director Harold Varmus to disband it. See *id.* The rationale underlying this proposal is that "most proposals today are straightforward enough that they can be reviewed directly by the Food and Drug Administration." *Id.* One intended outcome is more reliance on IRBs (rather than RAC), though reliance on IRBs has been the source of both concern and public criticism:

Abbey S. Meyers, Pres. of the National Organization for Rare Disorders, rejected Varmus's contention that institutional review boards at the universities where gene therapy experiments are conducted can be counted on to weed out unworthy studies. Those boards have neither the expertise nor the incentive to critically assess gene therapy experiments ... They are being reviewed by people who don't know anything about it but are desperate for their institution to become a gene therapy center. ... We have seen informed consent forms approved by IRBs that are unbelievable ...

Id. It is important to note, however, that RAC will continue one of its major missions maintenance of a registry of all gene therapy experiments underway in the country. See *id.*

clinical aspects of medicine, such as the American Medical Association and the National Hospital Association.

Even if enacted, reforms that conclusively control the quality of predictive genetic testing services at the national level through restrictions on their delivery—though a considerable improvement—still would not be adequate. The burgeoning nature of the biotechnology industry and the field of biomedical science mandates that there be no assumption of compliance with and enforcement of such regulations. Instead, public health officials must assume that consumers will have access to genetic testing and that genetic information will be generated in an increasing fashion. Accordingly, reforms such as those proposed above must be accompanied by the introduction of a regulatory infrastructure to protect consumers from abusive uses of genetic information. Without such reform, “[a]nswers to the next series of clinical questions may be jeopardized by the injudicious use of genetic testing by physicians and continued concern about the possibility of discrimination on the basis of the results.”²⁵⁸

National legislation governing the use of genetic information by insurers also is needed to overcome both regulatory disparities between the states and the preemptive effect of the Employee Retirement Income Security Act of 1974 (ERISA).²⁵⁹ Otherwise, those who choose to undergo genetic testing while a resident of a state limiting the use of genetic information may find themselves unable to obtain insurance coverage when they move to another state.²⁶⁰ Such regulation has been introduced to prevent employers from discriminating on the basis of genetic information.²⁶¹ Also, legislation

258. Olopade, *supra* note 177, at 1455.

259. 29 U.S.C. §§ 1001-1461 (1994). “Health care insurance may be declared an employee benefit when employers self-insure, thereby subjecting the insurance provided to regulation under ERISA.” Malinowski, *supra* note 125, at 351 n.143; *see also* Roberta Casper Watson, *Fiduciary Issues in the Administration of Health Plans*, in ALI-ABA COURSE OF STUDY MATERIALS: FIDUCIARY RESPONSIBILITY ISSUES UNDER ERISA—1996, June 6, 1996, at 1007. Though recent federal cases have held that ERISA preemption is not an absolute defense to claims of medical malpractice, the statute generally has been interpreted to preempt state laws and regulations. *See* Malinowski, *supra* note 125, at 351 n.143.

260. *See* NBC *Nightly News* (NBC television broadcast, July 20, 1996), available in 1996 WL 10302511 (“Although Ruth wants a genetic test, she says she doesn’t dare, because each state has different rules when it comes to privacy. RUTH: If I’ve, while in New Jersey, gone ahead and done this—the genetic testing, and then at a later point we move, I’ve exposed myself.”).

261. In March 1995, the EEOC issued a new compliance manual, in which it included people who experience discrimination due to their genetic profiles for protection under the Americans with Disabilities Act (ADA), 42 U.S.C. §§ 12101-12213 (1994). *See*

has been proposed to place similar restrictions on insurers. This legislation includes the nondiscrimination provision in the health insurance reform bills that address genetic information and that were passed by the House and Senate during the last Congress.²⁶² In August 1996, President Clinton signed a version of these bills into law as the Health Insurance Portability and Accountability Act.²⁶³

Nevertheless, absent comprehensive consumer protection from genetic discrimination at the federal level, the protection of citizens and regulation of the insurance industry rests well within the purview of the states' public health responsibilities. Moreover, while Congress has been contemplating protective measures, states have been enacting them.²⁶⁴ Some states, including Massachusetts, are contemplating innovative measures.²⁶⁵ State public health officials should promote

EEOC COMPLIANCE MANUAL, *supra* note 127, § 902.8(a); *see also* Annas, *supra* note 14, at 19-22 (discussing genetic testing and potential privacy concerns); Lord, *supra* note 22, at 86; Richard Saltus, *US Ruling Bars Discrimination Based on Genes; Prohibits Employer from Denying Job Because of Predisposition to Illness*, BOSTON GLOBE, Apr. 11, 1995, at 4 ("Now, a federal commission has ruled that employers cannot deny a job or fire someone because of his genes. The ruling covers only employment, not health or life insurance, but consumers and researchers say it's an important precedent."). Genetic alterations are deemed "disabilities" in that those who have them are perceived as having a physical or mental impairment that substantially limits one or more of a person's major life activities. *See* Lord, *supra* note 22, at 86. An employer may, however, be able to exclude a category of employees from certain exposure based upon his or her genotype, and "section 501(c) of the ADA permits employers to observe the terms of a bona fide health insurance plan based on underwriting risks and classifications, provided there is no 'subterfuge' to evade the purposes of the act." *Id.*

262. *See supra* note 82 (addressing Kassebaum-Kennedy sponsored bill). *But see* Piercey, *supra* note 127, at 1 (reporting that, based upon alleged "internal documents" from the Health Insurance Association of America (HIAA), "Kennedy claims that, while genetic information and other health factors could not be used to deny coverage, they might be used to 'design' coverage").

263. Pub. L. No. 104-191, 110 Stat. 1936 (1996); *see also supra* note 127 (discussing the Act).

264. As of July 1996, notable state efforts included:

1. *laws barring both employers and insurance companies* from discriminating against individuals based upon the results of genetic testing enacted in New Hampshire, New York, Oregon, and Wisconsin;
2. *laws prohibiting employers* from using genetic information to discriminate against employees or job applicants enacted in Iowa and Rhode Island; and
3. *pending bills* in California, Massachusetts, Michigan, New Jersey, and Pennsylvania.

See New York Bill Prohibiting Genetic Discrimination Signed Into Law, WEST'S LEGAL NEWS, July 31, 1996, at 7845, available in 1996 WL 423290; *see also* Genetic Testing by Employers, Labor Organizations, and Licensing Agencies, 1996 N.Y. Laws Ch. 204, § 1.

265. *See supra* note 188. Massachusetts is contemplating (1) delegation of ongoing quality assessment and implementation of effective informed consent standards to the

legislation to protect consumers in the absence of federal legislation and supplement any federal protections that are eventually enacted. State responsiveness and ingenuity is especially needed to address informed consent for genetic testing and the broader issue of genetic counseling.²⁶⁶ The best state solutions to these challenges ultimately could become national ones.

When proceeding to implement reforms such as those identified above, legislators and medical and public health officials must anticipate the reaction of the biotechnology industry and proceed with market sensitivity.²⁶⁷ At both the state and federal levels, the biotechnology industry is recognized as an important sector in the

Department of Public Health, (2) consumer control over genetic information, such as the option to have this information separated from medical records, and (3) a five-year moratorium on the use of genetic information by insurers coupled with a provision that would place the burden on insurers to have actuarial data in hand to establish the validity and predictability of genetic tests before they may use the resulting information in any way. See Observation by Michael Malinowski, Member of the Massachusetts Legislature's Special Committee on Genetic Information Policy; see also Richard Saltus, *Genetic Privacy Bill in Works*, BOSTON GLOBE, Feb. 2, 1997, at B2.

266. The Draft Interim Principles identified by the ELSI Task Force include the following:

Principle III-5: Informed consent for a validation study must be obtained whenever the specimen can be linked to the subject from whom it came.

Under FDA regulations informed consent is needed in the investigational stage of device development, except when waived by an IRB.

....

Principle III-7: Health care providers must describe the features of the genetic test, including potential consequences, to potential test recipients prior to the initiation of predictive testing in clinical practice.

The informed consent process contributes importantly to the education of people who are offering testing.

The responsibility for providing information to the individual lies with the referring provider, not with the laboratory performing the test.

ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 27-28. For a discussion of patient autonomy in the context of genetic counseling, see Robert Wachbroit & David Wasserman, *Patient Autonomy and Value-Neutrality in Nondirective Genetic Counseling*, 6 STAN. L. & POL'Y REV. 103 (1995).

267. See Meeting Minutes, *supra* note 1, at 2 (

Dr. Holtzman commented on the importance of resolving regulatory and other uncertainties, because genetic tests may not reach the marketplace unless venture capitalists have the confidence to invest sufficient funds in their development. For small firms which lack the financial resources and regulatory expertise required to bring a test to market, a joint venture with a large pharmaceutical firm may be the only practical solution.

United States's economic future,²⁶⁸ and many of the products being developed by that sector could greatly improve public health. However, the diverse nature of the biotechnology industry and its multitude of products should enable reforms necessary to ensure the responsible application of predictive genetic testing services to be enacted, assuming a market-sensitive approach is followed.

Initiatives to enact such reforms actually may benefit from industry insight or prompt industry to introduce self-reforms that are equally effective. Although the guiding incentive of the industry ultimately is profit, that incentive may be used to bring about the consumer-protection regulation that is needed. For example (albeit to preserve and increase consumer demand) biotechnology companies have joined patient-advocacy groups in lobbying policy makers to reform the FDA review process²⁶⁹ and prohibit insurance companies from using genetic information.²⁷⁰ Similarly, OncorMed developed its elaborate, thoughtful genetic testing protocols at great expense to "Coase around" FDA regulations that impede access to consumers and, at times, unduly impede the advancement of life science. Whichever proposals ultimately are adopted to regulate the commercialization of predictive genetic testing services, public health officials should make heavy reference to supportive provisions from responsible protocols developed by the biotechnology industry and its academic allies both to win industry support and to quell opposition.

VI. CONCLUSION

In *Oedipus Rex*, the character Tiresias has the ability to see into the future as if it were yesterday. Tiresias's divine gift of vision, however, gives him no ability to change what he sees. In his words to King Oedipus, "Wisdom is a curse when wisdom does nothing for the man that has it."²⁷¹ Without established PPV, predictive genetic tests offer much less certainty than Tiresias's vision. Although biomedical

268. See generally Malinowski & O'Rourke, *supra* note 20 (noting that technology is becoming commercially viable, and companies are investing more resources to enforce their patents).

269. See MICHAEL J. MALINOWSKI, INTERNATIONAL GUIDE TO THE LAW, BUSINESS AND REGULATION OF BIOTECHNOLOGY (forthcoming 1997).

270. See Piercey, *supra* note 127, at 1 ("Biotechnology companies and patient advocacy groups lobbied lawmakers to include language barring genetic discrimination because many see it as a necessary precondition for the widespread use of genetic testing.").

271. SOPHOCLES, OEDIPUS THE KING 37 (Stephen Berg & Diskin Clay trans., Oxford Univ. Press ed. 1978).

science carries the promise of therapeutics and gene therapies, in their absence, the present inability to change the future remains.

This Article has analyzed the commercialization of predictive genetic testing for BRCA alterations linked to breast and ovarian cancer. Beyond addressing this contemporary and pressing problem, the objective has been to illustrate the public health implications of the premature commercialization of this technology, to identify regulatory shortcomings, and to introduce proposals for change. As has been emphasized throughout this Article, BRCA testing simply marks the beginning of widespread predictive genetic testing.

Predictive genetic tests without established PPV are unacceptable for broad commercialization. Such tests are highly subject to misinterpretation by those who undergo them *and* by the health care providers who make them available. They are the equivalent of biological tarot cards.



Public health officials must directly address the issue of quality assurance for predictive genetic testing services. They must introduce consumer safeguards tailored to this innovative technology and, more importantly, they must enforce them. This Article has proposed numerous regulatory reforms to control access to and the quality of predictive genetic tests. Many of these proposals center on remaining faithful to the practice of good medicine.

Advances in biomedical research offer many patients hope, not harm. The threat that accompanies this medical technology comes from the temptation to use it prematurely and irresponsibly. Just as physicians should not sell a drug or diagnostic to their patients that they do not understand (and, therefore, cannot measure the benefits of), physicians should not be making research-stage predictive genetic tests available without the precautions necessary to avoid doing harm.

Predictive genetic testing simply is at the vanguard of an era of unprecedented progress in medicine attributable to genetic science. For centuries, the adage "First, do no harm" has guided the medical profession. The profession and the adage have endured jolting advances in medical technology—from anesthesia, to antibiotics, to vaccinations. Similarly, if contemporary public health officials look to this adage, they will find guidance. Promoting and enforcing the practice of responsible medicine continues to be the answer.

APPENDIX I

Excerpt from Letter Summary of the OncorMed Protocol²⁷²

Patients who are eligible for testing under this protocol are:

1. persons with breast and/or ovarian cancer who have two or more first- or second-degree* blood relatives (related through a single lineage) with either breast or ovarian cancer,
2. persons with breast and/or ovarian cancer which developed at an early age (<45 years),
3. persons with breast and/or ovarian cancer with multiple primary cancers or bilateral disease,
4. males who develop breast cancer at any age,
5. relatives of persons with documented mutations in the BRCA1 or BRCA2 gene.

* first-degree relative: parent, siblings, offspring; second-degree relative: aunt, uncle, grandparent, grandchild, niece, nephew, half-sibling

Patients who may not be tested are:

1. a person under the age of 18 years,
2. a cognitively impaired person or one who is unable to provide informed consent,
3. someone who has a psychological condition precluding testing.

To test a patient under this protocol, the physician would agree to:

- ◇ Call in or fax the family history to OncorMed before testing. Pathological verification of the history should be obtained whenever possible.
- ◇ Identify a genetic counselor to evaluate the family history, explain inheritance, discuss the benefits, risks, limitations, and psychosocial impact of testing; a medical and surgical oncologist to discuss management options; and a mental health specialist to help in the decision to test, to provide support during the testing process, or to help adjust to the results. The patient should be offered these referrals both

272. This summary was taken from the Hereditary Breast Cancer Testing Packet received from OncorMed in January 1997. OncorMed, Inc. may be contacted at 205 Perry Parkway, Gaithersburg, Maryland 20877. The company may also be contacted by telephone at 301-208-1888 or facsimile at 301-926-6329.

before and after testing. OncorMed can help you locate a genetic counselor in your area, if needed.

- ◇ Ensure that informed consent is obtained and that the patient receives pre- and post-test counseling by one or more professionals knowledgeable about the genetics and management of hereditary breast cancer syndromes.
- ◇ Give the test results to the patient in person and develop a management plan with the patient.
- ◇ Refer the patient to the specialists you have identified as needed, provide psychological support, and assist in informing relatives if appropriate.

We have provided a number of items which may help you counsel and test patients under this protocol.

- ◇ A testing flow diagram which outlines the protocol and which you can keep as part of your records to document progress through the testing process.
- ◇ A physician Q&A with information on BRCA1 and BRCA2 and on testing patients.
- ◇ A patient Q&A describing testing which can be given to patients. Encourage the patient to take the Q&A and the consent home to review prior to agreeing to be tested.
- ◇ Counseling checklists which you can use to be sure all relevant information is covered during the pre-and post-test counseling sessions and which can be given to the patient as a summary of the counseling.
- ◇ A clinical history form and consent which should be signed and returned with the blood sample if the patient agrees to testing.

APPENDIX II²⁷³

ELSI TASK FORCE DRAFT INTERIM PRINCIPLES FOR LABORATORY QUALITY

The ELSI Task Force identified 4 categories for considerations related to laboratory quality: (1) biologic materials and components, meaning the reagents and equipment used by the laboratory; (2) laboratory start-up, meaning the introductions of new tests; (3) laboratory practice,

273. ELSI TASK FORCE ON GENETIC TESTING, *supra* note 1, at 16-22.

meaning the actual performance of tests, personnel, internal quality control, and quality assurance mechanisms; and (4) laboratory oversight, meaning proficiency testing, accreditation, and inspection. The Task Force issued the following principles:

A. *Components and Biologic Materials*

Principle II-1: A genetic test must be analytically validated for each analyte it is intended to measure. It is ultimately the responsibility of each laboratory director to ensure analytic validity.

... [T]here is minimal external oversight of the components used in genetic testing, except for those in FDA-approved kits or other devices. Although the Task Force is considering policies to change this picture, for the moment the laboratory supervisor must be responsible for assuring the performance characteristics of the components used in the laboratory's testing repertoire. Under the authority of CLIA (or of states that are at least as rigorous as CLIA), government surveyors are supposed to determine whether laboratories have developed new tests and, if so, to then review their data for analytic validation. . . .

Principle II-2: Appropriate specimens from patients, carriers, and controls should be available through a centralized system in order to facilitate their availability to aid in analytical validation, improving quality, or other needs.

....

B. *Start-Up*

Principle II-3: Laboratories can offer new genetic tests only after their analytical and clinical validity have been established by that laboratory or elsewhere.

....

Principle II-4: Before routinely offering genetic tests that have been clinically validated, a laboratory must conduct a pilot phase in which it verifies the performance characteristics of its test.

....

Principle II-5: Prior to beginning routine patient testing, the laboratory must review and evaluate the data collected in the pilot phase.

....

Principle II-6: Research laboratories that provide physicians with results of genetic tests, which may be used for clinical decision

making, must validate their tests and be subject to the same internal and external review as other clinical laboratories.

....

C. *Practices*

... The potential for errors in referral, the choice of an appropriate test, the probabilistic, predictive, and conditional nature of test results place a greater burden on communication between the laboratory and the provider ordering and/or receiving results than is the case for many other types of tests. . . .

Principle II-7: Because of the complexities in assessment and interpretation, requisitions for genetic tests require more intake information than those for most other clinical laboratory tests.

... If information that is critical to the performance or the interpretation of the test cannot be obtained, the specimen should be rejected. . . .

Principle II-8: Genetic test results must be written by the laboratory in a form that is understandable to the nongeneticist health care provider.

... Laboratory reports must include sufficient information in order for the referring provider to interpret the results appropriately to the person tested or, in the case of minors, to their parents. . . .

Principle II-9: Personnel serving as directors or technical supervisors of genetic testing laboratories must have formal training in human and medical genetics.

....

Principle II-10: Training programs for laboratory technicians/technologists should include more human and medical genetics content than is currently available.

... Several formal training programs for cytogenetics technical staff are available, but there are only one or two certificate—or diploma—track genetics training programs for technicians or technologists in the U.S. . . .

....

D. *External Review*

Principle II-11: A national accreditation program for laboratories performing genetic tests, which includes on-site inspection and proficiency testing, is needed to promote standardization.

....

Principle II-12: Genetic testing laboratories must participate in proficiency testing (PT) programs for each of its tests, if available. When no relevant proficiency testing programs exist, laboratories must, whenever possible, participate in inter-laboratory comparison programs and help develop them if none exist in their particular area of testing. Proficiency testing programs should be broadly based since the number of genetic disorders is very large and the analytical approaches to testing are numerous. Laboratories and inspectors should use PT results to help a laboratory improve its quality.

....

In mandatory PT programs, some punitive action is taken if laboratories that "fail" do not improve their performance on subsequent rounds.