


Medical Implications of the Genetic Revolution

Monique K. Mansoura

Francis S. Collins

Follow this and additional works at: <http://digitalcommons.law.umaryland.edu/jhclp>

 Part of the [Bioethics and Medical Ethics Commons](#), [Congenital, Hereditary, and Neonatal Diseases and Abnormalities Commons](#), and the [Health Law Commons](#)

Recommended Citation

Monique K. Mansoura, & Francis S. Collins, *Medical Implications of the Genetic Revolution*, 1 J. Health Care L. & Pol'y 329 (1998).
Available at: <http://digitalcommons.law.umaryland.edu/jhclp/vol1/iss2/3>

This Article is brought to you for free and open access by DigitalCommons@UM Carey Law. It has been accepted for inclusion in Journal of Health Care Law and Policy by an authorized administrator of DigitalCommons@UM Carey Law. For more information, please contact smccarty@law.umaryland.edu.

MEDICAL IMPLICATIONS OF THE GENETIC REVOLUTION*

MONIQUE K. MANSOURA, PH.D.**
FRANCIS S. COLLINS, M.D., PH.D.***

I. THE HUMAN GENOME PROJECT: ITS PROMISE AND CHALLENGES

The Human Genome Project (HGP), the multi-disciplinary, multi-institutional, multi-million dollar effort aimed at mapping and sequencing the entire three billion base pairs of the human genome,¹ will be completed in less than a decade.² A primary impetus of this monumental task, which has mobilized the efforts of thousands of scientists and generated the enthusiastic support of Congress, is to provide the biomedical research community with the tools to identify

* The ideas and opinions expressed in this paper are those of the authors' only and do not represent any position or policy of any federal agency, or any other institution or organization to which they are affiliated.

** Postdoctoral Fellow in the laboratory of Dr. Melissa Ashlock at the National Human Genome Research Institute, where she conducts research in the field of cystic fibrosis. Dr. Mansoura received her M.S. in Human Genetics (1992) and Ph.D. in Biomedical Engineering (1996) from the University of Michigan where she was awarded a National Science Foundation Graduate Fellowship. The author wishes to thank Lorry Brody, Ph.D., David FitzGerald, Ph.D., and Larry Fenner, Ph.D. for their critical reviews of this manuscript and the insightful discussions.

*** Director of the National Human Genome Research Institute at the National Institutes of Health (NIH). Dr. Collins oversees a fifteen year project directed at mapping and sequencing all of the human genes. He joined NIH in 1993 after serving as a member of the faculty at the University of Michigan and completing a fellowship in human genetics at Yale. His research led to the identification of genes responsible for cystic fibrosis, neurofibromatosis and Huntington's disease. He is a member of the Institute of Medicine in the National Academy of Sciences.

1. "Within the nucleus of every human somatic cell, in two versions distributed over 23 chromosomes [one set maternally derived, and the other paternally derived], lies a genetic instruction tape embodied in DNA [deoxyribonucleic acid]." See Francis S. Collins, *Sequencing the Human Genome*, 32 HOSP. PRAC. 35, 35 (1997). Each set of chromosomes contains three billion bits of information, genetic sequence data, spelled out in a four letter code. See *id.* Each cell uses this information to create the proteins which do the work necessary to carry out the functions of that particular cell type. See *id.* "[T]he sequence, is 99.9% identical from one individual to another. This makes it reasonable to speak of a human genome, at least for the purposes of determining a complete representative sequence. . . ." *Id.*

2. See *id.*; National Human Genome Research Institute, National Institutes of Health (visited Jan. 14, 1998) <<http://www.nhgri.nih.gov/HGP/>>. Two recent reviews also provide an overview of the HGP. See generally Leslie Fink & Francis S. Collins, *The Human Genome Project: View from the National Institutes of Health*, 52 J. AM. MED. WOMEN'S ASSOC. 4, 4-7 (1997); Ari Patrinos & Daniel W. Drell, *The Human Genome Project: View From the Department of Energy*, 52 J. AM. MED. WOMEN'S ASSOC. 8 (1997).

the molecular basis of virtually all diseases, so that ultimately this information can be used by scientists and physicians to provide early detection and to develop and evaluate treatment strategies and cures for affected individuals. Since genetic predisposition plays an important role in almost every disease, albeit to widely varying degrees, the HGP promises to have a significant medical benefit for everyone. However, the promise of the HGP is tempered by concern about the potential misuses of genetic information. Fear of discrimination by insurers and employers has already limited some potential benefits as some individuals are refusing to participate in research and declining testing for fear of discrimination and loss of privacy.³ Similarly, the improper use of genetic information in legal contexts threatens the realization of the full medical benefit of the science.⁴ This has united patient advocacy groups, such as the National Action Plan on Breast Cancer (NAPBC), and researchers at the National Human Genome Research Institute (NHGRI) in efforts to prevent such misuse.⁵

By all scientific measures the HGP has been a resounding success thus far.⁶ The exponential rate at which maps and technologies have been created and new genomic sequences are being deposited into Genbank⁷ is having a significant impact on the identification of the molecular basis of genetic diseases - an early, but invaluable step in the path to understanding the underlying pathophysiology and developing treatments and cures. Current estimates indicate that a new gene is identified and entered into the database every 2.5 days.⁸ As an example of the accelerated rate of gene discovery, it is insightful to compare efforts of gene hunting by positional cloning⁹ before and

3. See *infra* notes 70-109 and accompanying text.

4. See *id.*

5. The Hereditary Susceptibility Working Group of the NAPBC has made this topic a major focus of interest. The Hereditary Susceptibility Working Group, The National Action Plan on Breast Cancer (last modified Jan. 8, 1997) <<http://www.napbc.org/napbc/heredita.htm>>.

6. Francis S. Collins & David Galas, *A New Five-Year Plan for the U.S. Human Genome Project*, 262 *SCIENCE* 43, 43, 46 (1993).

7. GenBank is the NIH genetic sequence database, an annotated collection of all publicly available DNA sequences. There are approximately 1,053,500,000 bases in 1,766,000 sequence records as of October 1997. National Center for Biotechnology Information, (last modified Oct. 20, 1997) <<http://www.ncbi.nlm.nih.gov/Web/Genbank/index.html>>.

8. Mark Boguski, Lecture at the National Institute of Health on Current Topics in Genome Analysis (Nov. 4, 1997).

9. Positional cloning is the method of locating a gene based on its position in the genome without necessitating knowledge of the functional product. See Soumitra Ghosh & Francis S. Collins, *The Geneticist's Approach to Complex Disease*, 47 *ANN. REV. MED.* 335 (1996). It depends upon linkage analysis in which a DNA marker identifying a particular location within the genome is found to cosegregate with disease in one or more families. See *id.* If such a marker is identified, it indicates that the altered genetic sequence involved in the

after the HGP was initiated. The cystic fibrosis (CF) gene was identified in 1989, before the HGP was formally initiated, after an arduous ten-year collaborative effort with an overall expense of roughly fifty million dollars. In striking contrast, the gene abnormality that causes some cases of Parkinson's disease was identified in 1997 within only nine days.¹⁰ Using samples collected from a large family with a high incidence of Parkinson's, researchers at the NHGRI obtained linkage to a region of the genome containing approximately 100 genes. One of the genes already placed in this interval was alpha-synuclein, which was an excellent candidate for being a Parkinson's disease gene, and was found to harbor a subtle mutation in the Parkinson's disease families.¹¹ As the HGP reaches fruition, this accelerated path to gene discovery will be the rule rather than the exception.

What value does the identification of a genetic basis of disease have for an individual and their family? It is the goal of this paper to delineate the role that genetic information plays in the onset of genetic disease and to identify the potential medical implications for an individual and for family members. The link between a sequence alteration in the genome of an individual and the possibility of future disease is complex and poorly understood in all but a few cases. A review of the fundamental principles of genetics and an update on the realities of what the science can offer ensures a solid foundation for ethical discussions and legal debates. Potential negative consequences of the misuse of genetic information and the depth of the impact it may have on the lives of individuals and their families demands that any discussion be grounded in scientifically-based analyses. We must be cognizant that we are dealing with a continuously expanding base of information and be aware of new discoveries which may inform our deliberations. We should also challenge ourselves to attempt to foresee the technologies and discoveries that lie ahead in order to minimize unnecessary burdens on future generations. A recent editorial in *Science* discussing the breakthroughs of 1997 states that

disease is "linked," or nearby, in genetic terms. See *id.*; see also Francis S. Collins, *Of Needles and Haystacks: Finding Human Disease Genes by Positional Cloning*, 39 CLINICAL RES. 615 (1991) (detailing information about the positional cloning strategy); Francis S. Collins, *Positional Cloning Moves From Perditional to Traditional*, 9 NATURE GENETICS 347 (1995).

10. See Mihael H. Polymeropoulos et al., *Mutation in the Alpha-Synuclein Gene Identified in Families with Parkinson's Disease*, 276 SCIENCE 2045 (1997); see also generally Robert L. Nussbaum and Mihael H. Polymeropoulos, *Genetics of Parkinson's Disease*, 6 HUM. MOLECULAR GENETICS 1687 (1997).

11. See NHGRI Media Release: Parkinson's Disease (visited Feb. 6, 1998) <<http://www.nhgri.gov/DIR/LGDR/PARK2/audio.html>>.

[I]ike the 4-minute mile, which was once believed to be the limit of human running capacity, preconceived limits in several scientific fields were made obsolete this year This year's advances demonstrate once again that one should never say never in science and that the exercise of imagining what could come to pass may be worth practicing.¹²

A. *Molecular Basis of Genetic Disease*

Genetic diseases result from a sequence alteration in one or more genes and can be classified into three major categories: chromosomal, single gene (monogenic) and polygenic.¹³ In many instances, the occurrence of the disease results from a combination of genetic and environmental factors - that is, genetic alterations are frequently *predisposing, not predetermining*, and require additional triggers. We need to challenge genetic reductionism, the philosophy that all diseases, traits, and behaviors are determined solely by our genetic constitution.

Chromosomal disorders are the result of the addition or deletion of parts of entire chromosomes and are typically identified using cytogenetic techniques. Recent technological advances in spectral karyotyping¹⁴ are significantly improving the sensitivity of detection of these abnormalities. Monogenic and polygenic disorders involve alterations in one or more genes, respectively. These alterations can occur in a variety of ways including insertions, deletions, or substitutions of one or more base pairs. For monogenic diseases it is not unusual for "a minute genotypic difference [to] have profound phenotypic effects. A classic example is sickle-cell anemia, in which precisely one A (the nucleotide, or base, adenine), among three billion code letters, has been replaced by a T (thymine), affecting the instructions for β globin."¹⁵ More recent examples include cystic fibrosis¹⁶ and achondroplasia,¹⁷ the most common type of short-limbed dwarfism. Still, identification of a gene mutation associated with an

12. Floyd E. Bloom, *Breakthroughs 1997*, 278 *SCIENCE* 2029, 2029 (1997).

13. See THOMAS D. GELEHRTER ET AL., *PRINCIPLES OF MEDICAL GENETICS* 3 (2d. ed. 1998).

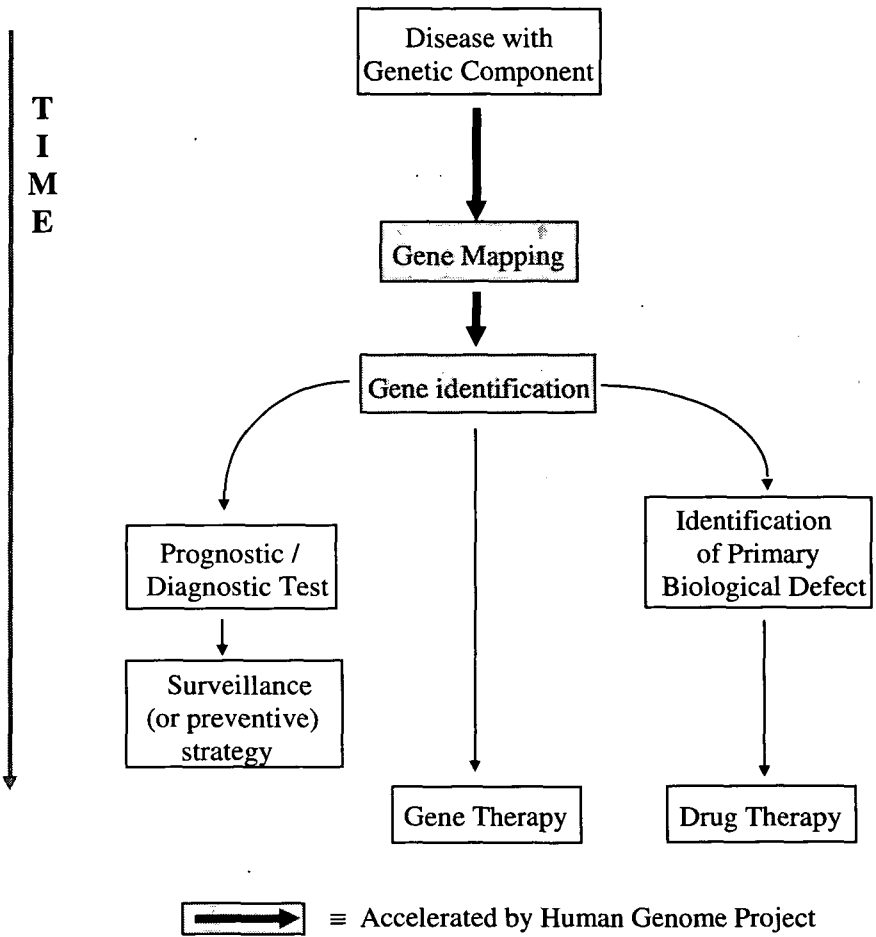
14. Spectral karyotyping is a technique which uses multicolor fluorescent dyes and spectral imaging to simultaneously distinguish each human chromosome by a different color. See Evelin Schröck et al., *Multicolor Spectral Karyotyping of Human Chromosomes*, 273 *SCIENCE* 494 (1996) (initial report describing this new cytogenetic technique); see also Tim Veldman et al., *Hidden Chromosome Abnormalities in Haematological Malignancies Detected by Multicolour Spectral Karyotyping*, 15 *NATURE GENETICS* 406 (1997).

15. Collins, *supra* note 1, at 35; see GELEHRTER ET AL., *supra* note 13, at 98 (discussing further the consequences of this genetic mutation).

16. See generally John R. Riordan et al., *Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA*, 245 *SCIENCE* 1066, 1066 (1989).

inherited disorder, while significant, is only an early step in the elucidation of the pathophysiology and the development of treatments and/or cures (Figure 1).¹⁸

Figure 1 - Patterns of progress in genetic medicine show the influence the Human Genome Project is having on overall rates of discovery



17. See Rita Shiang et al., *Mutations in the Transmembrane Domain of FGFR3 Cause the Most Common Genetic Form of Dwarfism, Achondroplasia*, 78 CELL 335, 335 (1994).
18. Figure one adapted from Collins, *supra* note 1, at 36.

The consequence of the sequence alteration in the gene is often the aberrant regulation and/or function of the encoded protein.¹⁹ Understanding the physiological role of the encoded protein is often critical to the development of treatments and cures. However, the promise of gene therapy offers a means to use the gene as a therapeutic agent, and perhaps bypass acquiring detailed knowledge of the underlying pathophysiology of the disorder (Figure 1). Most likely, as has been the situation for cystic fibrosis, scientists will pursue in parallel both gene therapy and traditional pharmacological approaches and a combination of treatment strategies will be applied to improve the quality of life of affected individuals.

B. Genetic Testing: Goals, Methods, and Limitations

All of us carry an estimated five to fifty significant genetic alterations. Genetic disease should not be thought of as the unfortunate fate of relatively few individuals who have been affected by rare inherited disorders. With our rapidly expanding understanding of the role of genes in common disorders such as many forms of cancer, heart disease, diabetes, mental illness, it seems more likely that in the future virtually all of our lives will be touched by the genetic revolution. *Genetic testing* is the means which allows such sequence alterations to be identified. In a clinical context, genetic testing is applied in several settings. The first widespread application has been in prenatal diagnosis where chromosomal abnormalities or specific mutations in known genes are tested for. This may be in the context of advanced maternal age (looking for Down syndrome) or the test may be more specific if one or both of the partners has a family history of a genetic disease such as cystic fibrosis (CF).

Genetic testing is also carried out to assist the diagnosis of disease for individuals who are currently ill, such as a DNA or cytogenetic test to look for fragile X syndrome²⁰ in a mentally retarded male. The newest area, but one in which we anticipate the greatest growth, is that of pre-symptomatic diagnosis - identifying individual risks of future illness in individuals who are currently healthy. It is this predictive capacity which sets this kind of genetic information apart from most

19. See generally Mahlon Hoagland & Bert Dodson, *The Molecules of Life*, 36 JUDGES' J. 11 (1997) (providing an informative lay discussion of the relationship between DNA and proteins).

20. See Lisa Chakrabarti & Kay E. Davies, *Fragile X Syndrome*, 10 CURRENT OPINION IN NEUROLOGY 142 (1997) (identifying that the Fragile X Syndrome is the single most common form of inherited mental handicap after Down's Syndrome, and the known cognitive dysfunction in Fragile X males includes visual-spatial abilities, deficits in short-term memory, visual-motor coordination, processing of sequential information, and attention).

other medical information, and is one of the unique features which justifies increased surveillance of clinical utility and the development of policies/legislation to minimize abuse. One consequence of this predictive capacity has been described as a "therapeutic gap."²¹ This situation arises when a disease can be diagnosed or predicted by genetic testing, yet no effective interventions are available to improve the outcome. Unfortunately, this is today's reality for most inherited diseases. The agonizing dilemmas this poses have been eloquently addressed by Dr. Nancy Wexler, primarily in the context of genetic testing for Huntington's disease (HD).²² She has also displayed remarkably accurate foresight in the discussion of the development of genetic tests for breast cancer, colon cancer, heart disease, and Alzheimer's disease.²³

In addition to the therapeutic gap, there are two other significant uncertainties which arise from the underlying complexity of genetic disease and thereby limits the value of predictive genetic test information. "Negative (normal) test results might not rule out future occurrence of the disease. . . . A positive test result might not mean the disease will inevitably develop"²⁴ and often offers little information to the individual regarding when disease onset will occur, and/or how severe the expression of the disease will be.²⁵

C. Underlying Complexity of Genetic Disease

Diagnosis of genetic diseases is often complicated by a number of factors which result in considerable clinical (phenotypic) heterogeneity.²⁶ "Clinical heterogeneity" refers to the variability in expression of a particular disease among those affected (e.g., the age of onset, the extent and severity of symptoms, impact on morbidity/mortality).

21. TASK FORCE ON GENETIC TESTING, NATIONAL INSTITUTES OF HEALTH - DEPARTMENT OF ENERGY, PROMOTING SAFE AND EFFECTIVE GENETIC TESTING IN THE UNITED STATES 2-3 (Neil A. Holtzman & Michael S. Watson eds., 1997) [hereinafter PROMOTING SAFE AND EFFECTIVE GENETIC TESTING].

22. See Nancy Wexler, *Clairvoyance and Caution: Repercussions from the Human Genome Project*, in THE CODE OF CODES: SCIENTIFIC AND SOCIAL ISSUES IN THE HUMAN GENOME PROJECT 211, 223 (Daniel J. Kevles & Leroy Hood, eds. 1992).

23. See *id.* at 242.

24. See PROMOTING SAFE AND EFFECTIVE GENETIC TESTING, *supra* note 21, at 3.

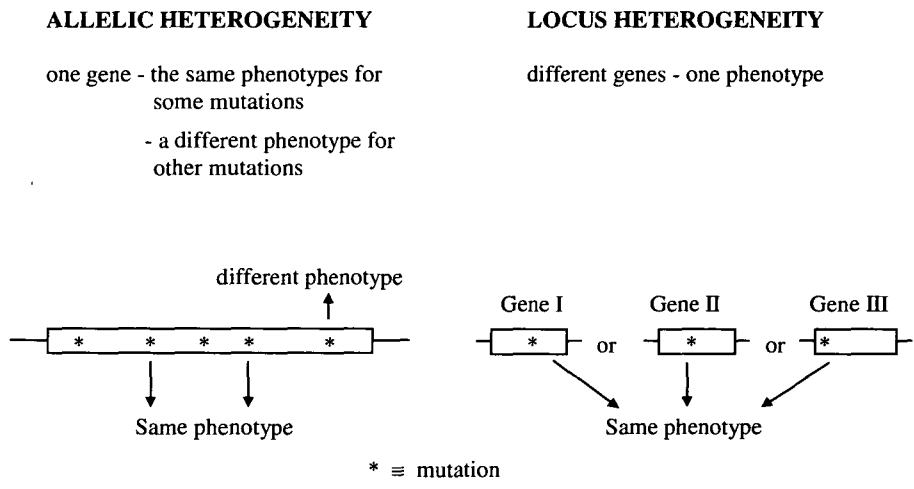
25. See *id.* Other factors such as analytical validity, while critical to the accuracy of a genetic test result, will not be discussed here. Details can be found in the Final Report of the Task Force on Genetic Testing. See *id.*

26. See Ulrich Wolf, *The Genetic Contribution to the Phenotype*, 95 HUM. GENETICS 127, 129 (1995); Ulrich Wolf, *Identical Mutations and Phenotypic Variation*, 100 HUM. GENETICS 305, 316 (1997). See generally Eric R. Fearon, *Human Cancer Syndromes: Clues to the Origin and Nature of Cancer*, 278 SCIENCE 1043, 1048 (1997).

The relationships between alterations in genetic sequences²⁷ and their clinical manifestations are most often complex and unpredictable, even in conditions with Mendelian²⁸ patterns of inheritance.²⁹ Realizing this daunting complexity, it is nonetheless appropriate to say that in many cases, beneficial information can be obtained by genetic testing, though what constitutes 'beneficial' is a highly individualistic determination.

In an effort to dissect clinical heterogeneity, and thus, the uncertainty that underlies the diagnosis/prognosis of genetic disorders, we will review each of the contributing factors. The first underlying source of phenotypic heterogeneity is *genetic heterogeneity*. This reflects the fact that different mutations in different genes can cause an identical or similar phenotype.³⁰ Genetic heterogeneity can be classified into two major categories: *allelic heterogeneity* and *locus heterogeneity* (Figure 2).³¹

Figure 2 : Underlying sources of genetic heterogeneity



27. See *supra* discussion accompanying note 1.

28. See GELEHRTER ET AL., *supra* note 13, at 4, 23-42 ("We define Mendelian diseases as diseases that are the result of a single mutant gene that has a large effect on phenotype and that are inherited in simple patterns similar to or identical with those described by Mendel for certain discrete characteristics in garden peas.")

29. See generally Ruth Hubbard & R. C. Lewontin, *Pitfalls of Genetic Testing*, 334 NEW ENG. J. MED. 1192 (1996).

30. See GELEHRTER ET AL., *supra* note 13, at 28.

31. See Wolf, *Identical Mutations and Phenotypic Variation*, *supra* note 26, at 305, and Figure 1.

“Allelic heterogeneity” refers to different mutations at one locus (gene).³² It is rare that every patient will have the identical sequence alteration (an exception is sickle cell anemia). More commonly, many different mutations are identified. For example, since it was cloned in 1989,³³ over 700 mutations have been identified in the cystic fibrosis (CF) gene.³⁴ Cystic fibrosis is “the most prevalent cause of severe, progressive lung disease in children and has become an important cause of lung-related morbidity and mortality in young adults.”³⁵ The encoded protein, a chloride channel known as CFTR (cystic fibrosis transmembrane conductance regulator), plays a critical role as a gatekeeper of salt and water transport in and out of cells which form the lining of various organs including the lungs and the intestines.³⁶ Altered salt and water transport in the lungs of CF patients is associated with thick mucous secretions and recurrent infections which lead to the destruction of lung tissues and respiratory failure.³⁷

The functional consequence of each particular mutation may have a variable influence on the severity of the disease (phenotype). In some cases, as with mutations in the CF gene, mutations can be categorized based on the molecular defect.³⁸ While all mutations result in reduced chloride channel function in some way, these classifications may have a significant impact on the avenue of research that is pursued and importantly, may dictate different treatment strategies based on genotype.³⁹ It may be insightful to compare the different classes of mutations in CFTR to various breakdowns of a bicycle to illustrate the value of genotype (i.e., mutation specific) based therapies (Table 1).

32. See GELEHRTER ET AL., *supra* note 13, at 28.

33. See John R. Riordan et al., *Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA*, 245 SCIENCE 1066, 1066 (1989).

34. See *Cystic Fibrosis Mutation Data Base* (last modified Apr. 6, 1998) <<http://www.genet.sickkids.on.ca/cftr/mutations.html>> (listing all currently identified mutations in cystic fibrosis transmembrane conductance regulator).

35. Michael J. Welsh et al., *Cystic Fibrosis in 3 THE METABOLIC AND MOLECULAR BASES OF INHERITED DISEASE* 3799, 3800 (Charles R. Scriver et al., eds., 7th ed. 1995).

36. See *id.* at 3799.

37. See *id.*

38. See generally Michael J. Welsh & Alan E. Smith, *Molecular Mechanisms of CFTR Chloride Channel Dysfunction in Cystic Fibrosis*, 73 CELL 1251 (1993).

39. See *id.* at 1253.

TABLE I: COMPARISON OF THE CONSEQUENCES OF A DEFECT IN A PROTEIN (CFTR) WITH THOSE OF A BICYCLE

Class	CFTR defect	Analogous bicycle defect
I	PROTEIN PRODUCTION (construction of the protein within the cell)	The bike is held up in production at the factory because the instruction manual for assembly is incomplete.
II	PROCESSING (delivery of the protein to the surface of the cell)	The handlebars are too wide and protrude through the shipping box. The box is held up at the shipping warehouse for safety reasons.
III	GATING (opening and closing of the channel)	The brakes are adjusted too tightly ⁴⁰
IV	CONDUCTION (rate of throughput of the channel)	The bike is stuck in low gear.

Assembly and delivery turn out to be formidable barriers within a cell for proteins involved in cystic fibrosis, breast cancer, and colon cancer. The crucial message here is that there is no value in having the tools to fix the brakes or the gears if the bike is stuck in the warehouse.

In contrast to disease-causing mutations, common sequence variations, most with absolutely no phenotypic consequences, occur on the average every 1000 base pairs. Continuing with the analogy, if the bicycle was painted a different color, it would still function properly. Sequence variation, which is observed just as often in individuals who do not exhibit disease as in those who do, is referred to as a *polymorphism*. Sometimes distinguishing a polymorphism from a disease mutation is not so easy, however. A gold-standard determination can come from a functional assay,⁴¹ but such assays are not currently available for many disease genes, since their function remains unknown.

40. The antithesis of cystic fibrosis is secretory diarrhea, as caused by the cholera toxin, in which an individual suffers from dehydration due to excessive secretion of salt and water in the intestines. *See id.* at 1252. This is analogous in the bicycle comparison to having no brakes at all. *See id.*

41. Cellular machinery converts a gene (blueprint) into a protein. Each protein performs one or more tasks, or functions. "Functional assays" are methods which are devel-

The second classification of genetic heterogeneity is *locus heterogeneity*. This refers to the fact that, for many diseases, more than one gene can be involved in disease onset. For example, inherited breast cancer has been associated with mutations in nearly a dozen genes (albeit to varying levels of risk), and the list is unlikely to be complete.⁴² These genes include BRCA1,⁴³ BRCA2,⁴⁴ p53⁴⁵ and PTEN/MMAC1.⁴⁶ Inherited mutations in BRCA1 and BRCA2 may account for as many as 5-10% of all breast cancer cases in the general population.⁴⁷ The epidemiological features of inherited, or familial breast cancer which distinguish it from spontaneous (non-inherited) cases are: (1) a strong family history of breast cancer in most cases, (2) early onset of the disease, and (3) the occurrence of other cancers in addition to breast cancer.⁴⁸

In the context of attempting to assess an individual's risk of disease, allelic and locus heterogeneity create a major technological problem for they necessitate screening one or more potentially large genes rapidly and accurately for all possible heterozygous mutations.⁴⁹ Current technologies often detect only a finite set of previously defined mutations. Efforts to screen an entire gene using these methods would be tedious and not very cost-effective. The emergence of DNA chip-based technology,⁵⁰ however, may provide a valuable new tool for high-throughput cost-efficient detection of genetic alterations.⁵¹ Ap-

oped to measure the function of the protein, ideally in a quantitative manner. Such assays are often critical to determining the consequences of mutations in the gene.

42. See generally Mark H. Greene, *Genetics of Breast Cancer*, 72 MAYO CLINICAL PROC. 54 (1997) (discussing clues to inheritable forms of cancer and the mapping of inherited cancer genes); Fearon, *supra* note 26.

43. See Yoshio Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1*, 266 SCIENCE 66 (1994).

44. See Richard Wooster et al., *Identification of the Breast Cancer Susceptibility Gene BRCA2*, 378 NATURE 789, 790 (1995).

45. See David Malkin et al., *Germ Line p53 Mutations in a Familial Syndrome of Breast Cancer, Sarcomas, and Other Neoplasms*, 250 SCIENCE 1233, 1234 (1990).

46. See generally Peter A. Steck et al., *Identification of a Candidate Tumor Suppressor Gene, MMAC1, at Chromosome 10q23.3 that is Mutated in Multiple Advanced Cancers*, 15 NATURE GENETICS 356, 361 (1997).

47. See Lawrence C. Brody & Barbara Bowles Biesecker, *Breast Cancer: The High-Risk Mutations*, 32 HOSP. PRAC. 59, 59 (1997).

48. See generally Greene, *supra* note 42, at 55.

49. See generally Joseph G. Hacia et al., *Detection of Heterozygous Mutations in BRCA1 Using High Density Oligonucleotide Arrays and Two-Colour Fluorescence Analysis*, 14 NATURE GENETICS 441 (1996).

50. See generally Graham Ramsey, *DNA Chips: State-of-the Art*, 16 NATURE BIOTECHNOLOGY 40 (1998).

51. See Mark Chee et al., *Accessing Genetic Information with High-Density DNA Arrays*, 274 SCIENCE 610, 610-13 (1996); Ann C. Pease et al., *Light-Generated Oligonucleotide Arrays for Rapid DNA Sequence Analysis*, 91 PROC. NAT'L ACAD. SCI. USA 5022, 5022-26 (1994).

plications to mutation detection in BRCA1,⁵² CFTR,⁵³ and HIV⁵⁴ have already proven feasible in the research laboratory, though issues of sensitivity, specificity, and cost must be further explored.

Another concept that is fundamental to understanding the process of predictive genetic testing is that of *penetrance*, which is "an all-or-none phenomenon that refers to the clinical expression, or lack of it, of the mutant gene."⁵⁵ This vital concept in discussions of pre-symptomatic genetic testing addresses the likelihood that a given sequence alteration will actually result in disease. For an individual, the probability of acquiring the disease being tested for is either 100% or 0% (i.e., either they will or will not get the disease). Yet penetrance estimates are, by necessity, statistical, and are most often based on high-risk family or population studies. Estimated risks may vary significantly depending on which segment of the population was examined. Some genetic alterations, such as those in the gene causing Huntington's disease (HD), are 100% penetrant⁵⁶ - if an individual lives long enough, the disease will be expressed. It is critical to realize that, in contrast to classical Mendelian disorders such as Huntington's disease, Tay Sachs, or cystic fibrosis, this level of predictive capacity in the context of multifactorial disease (which affect an overwhelmingly greater proportion of the general population and therefore will account for the majority of genetic tests in the future) will most likely be exceedingly rare due to the low penetrance of any individual mutation.

The penetrance of BRCA1 and BRCA2 mutations is currently the subject of controversy.⁵⁷ Initial estimates, based on studies of high-risk families calculated a 76-87% risk of breast cancer for carriers of genetic mutations in BRCA1.⁵⁸ Epidemiologists have rightly been cautious about risk estimates based on selective data sets such as those comprised of high-risk families. A more recent study examined samples from a population of more than 5000 Ashkenazi Jews and found a

52. See generally Hacia et al., *supra* note 49, at 441.

53. See generally Maureen T. Cronin et al., *Cystic Fibrosis Mutation Detection by Hybridization to Light-Generated DNA Probe Arrays*, 7 HUM. MUTATION 244 (1996).

54. See generally Michael J. Kozal et al., *Extensive Polymorphisms Observed in HIV-1 Clade B Protease Gene Using High-Density Oligonucleotide Arrays*, 2 NAT. MED. 753 (1996).

55. See GELEHRTER ET AL., *supra* note 13, at 27.

56. See *id.* at 27.

57. See, e.g., Doug Easton, *Breast Cancer Genes—What Are the Real Risks?*, 16 NATURE GENETICS 210 (1997).

58. See Doug F. Easton et al., *Breast and Ovarian Cancer Incidence in BRCA1-Mutation Carriers*, 56 AM. J. HUM. GENETICS 265, 270 (1995).

significantly lower value of breast cancer penetrance, 56%, for three specific BRCA1 or BRCA2 mutations.⁵⁹

Whether the penetrance estimate provided to a woman who tested positive for a BRCA1 or BRCA2 mutation is 56% or 87%, it nonetheless raises a multitude of complex and difficult decisions. As discussed in an editorial in the *New England Journal of Medicine* by former NIH director Bernadine Healy,

one of the effects of the discovery of the BRCA genes is the emergence of medical bookmaking and fortunetelling [Recent] reports should alert us to the limitations of the expanding medical practice of making gene-based statistical prophecies. The problem is not that the evolving information is not valuable,⁶⁰ but, rather, that it holds great potential for misapplication.⁶¹

Added to the uncertainty of the risk, is the "paucity of data to guide physicians in making follow-up recommendations to those who are found to be carrying a mutation."⁶² For example, while preventive strategies in high-risk individuals make intuitive sense, there is as yet little definitive evidence that increased surveillance (mammography) or prophylactic mastectomy will prevent ultimate death from breast cancer⁶³ in these high-risk women. "Information about the value of a preemptive strike against cancer in carriers of BRCA mutations is at best primitive"⁶⁴ This dictates that those considering testing understand the implications of both a positive or negative test result through a process of education and informed consent before testing. More research into testing decisions and their outcome is greatly needed.⁶⁵

Predictive genetic testing for colon cancer may offer greater clinical utility because there is stronger evidence that increased sur-

59. See Jeffrey P. Struewing et al., *The Risk of Cancer Associated with Specific Mutations of BRCA1 and BRCA2 among Ashkenazi Jews*, 336 NEW ENG. J. MED. 1401, 1401-02, 1407 (1997).

60. See Greene, *supra* note 42, at 62.

61. Bernadine Healy, *BRCA Genes—Bookmaking, Fortunetelling, and Medical Care*, 336 NEW ENG. J. MED. 1448, 1448 (1997).

62. Barbara Bowles Biesecker & Lawrence C. Brody, *Genetic Susceptibility Testing for Breast and Ovarian Cancer: A Progress Report*, 52 J. AM. MED. WOMEN'S ASS'N 22, 22 (1997).

63. See Deborah Schrag et al., *Decision Analysis—Effects of Prophylactic Mastectomy and Oophorectomy on Life Expectancy Among Women with BRCA1 or BRCA2 Mutations*, 336 NEW ENG. J. MED. 1465, 1470 (1997).

64. Healy, *supra* note 61, at 1448.

65. See Biesecker & Brody, *supra* note 62, at 22.

veillance and early detection are associated with improved outcome.⁶⁶ Already genetic testing for familial polyposis and hereditary non-polyposis colon cancer (HNPCC) has many advocates.⁶⁷ A recent report⁶⁸ identifies a sequence alteration in the adenomatous polyposis coli (APC) gene which is associated with an estimated twofold increase risk of colon cancer and occurs with high frequency (6%) in the Ashkenazi Jewish population, making it potentially the most common cancer-associated mutation known in a specific population. Large population-based studies are underway.⁶⁹ The results may have significant implications for large-scale screening recommendations.

It is anticipated that the majority of future genetic discoveries will involve sequence alterations with even lower penetrance values than that realized for BRCA1 or BRCA2. Genes which play a role in complex diseases such as heart disease, hypertension, diabetes, and psychiatric disorders will be identified, but the alleles associated with increased risk may each only confer a modest effect.

II. THE HUMAN GENOME PROJECT: BEYOND THE SCIENTIFIC CONCERNS

The designers of the HGP, in particular Dr. James Watson,⁷⁰ recognized that the information gained from mapping and sequencing the human genome would have profound implications for individuals, families, and society. To address the complex issues which arise from human genetics research, the Ethical, Legal and Social Implications (ELSI) Program was established from the onset as an integral part of the HGP.⁷¹

66. See generally Wylie Burke et al., *Recommendations for Follow-up Care of Individuals with an Inherited Predisposition to Cancer, I: Hereditary Nonpolyposis Colon Cancer* 277 JAMA 915 (1997).

67. See generally *id.*

68. See Steven J. Laken et al., *Familial Colorectal Cancer in Ashkenazim Due to a Hypermutable Tract in APC*, 17 NATURE GENETICS 79 (1997).

69. Personal conversation with Lawrence C. Brody, Investigator, Genetics and Molecular Biology Branch, National Human Genome Research Institute (Feb. 2, 1998).

70. Dr. Watson was the first Director of the Human Genome Project from 1989 to 1992 and winner of the Nobel Prize for codiscovering the double-helical structure of DNA in 1953. See Interview with James D. Watson (Oct. 22, 1991) available at *Dr. James D. Watson* (visited Apr. 10, 1998) <<http://www.achievement.org/autodoc/page/wat0int-1>>.

71. See Eric M. Meslin et al., *The Ethical, Legal, and Social Implication Research Program at the National Human Genome Research Institute*, 7 KENNEDY INST. ETHICS J. 291 (1997). Detailed information about the ELSI program can also be found at their web site. See *About the Ethical, Legal, and Social Implications of Human Genetics Research Program* (last modified Oct., 1997) <<http://www.nhgri.nih.gov/ELSI/aboutels.html#Whatis>>.

As the ELSI Program has evolved, four high priority areas of focus for research and policy activities have emerged:

1. Privacy and Fairness in the Use and Interpretation of Genetic Information. Activities in this area examine the meaning of genetic information and how to prevent its misinterpretation or misuse,
2. Clinical Integration of New Genetic Technologies. These activities examine the impact of genetic testing on individuals, families and society and inform clinical policies related to genetic testing and counseling,
3. Issues Surrounding Genetics Research. Activities in this area focus on informed consent and other ethical issues related to the design, conduct, participation in and reporting of genetics research,
4. Public and Professional Education. This area includes activities that provide education on genetics and related ELSI issues to health professionals, policy makers and the general public.⁷²

The Office of Policy Coordination (OPC) at NHGRI in conjunction with the ELSI Working Group, breast cancer advocates, and other consumer groups, has been focusing efforts on what we view as the two pillars of protection necessary to prevent the misuse of genetic information. The first pillar consists of the enactment of anti-discrimination laws, especially in the realm of health insurance and employment, and the second focuses on the assurance of privacy protections for individuals involved in genetic testing.

As mentioned previously, each of us has an estimated five to fifty serious misspellings or alterations in our DNA; thus, we could all be targets for discrimination based on our genes. The authors see this as fundamentally a civil rights issue.⁷³ No one gets to choose their DNA, and the DNA that we inherit is immutable. Policies that allow genetic information to be used to discriminate against individuals, families or groups are unjust. Of particular concern is the fear of losing jobs or health insurance because of a particular predisposition to a particular disease. These are already real concerns for many Americans. In a recent survey of people in families with genetic disorders, 22% indi-

72. See Meslin et al., *supra* note 71; see also ELSI website (last modified Oct., 1997) <<http://www.nhgri.nih.gov/ELSI/aboutels.html#Issue>>.

73. See Francis S. Collins, Presentation at Inaugural Meeting of the National Bioethics Advisory Commission (NBAC) (Oct. 4, 1996) (transcripts on file with the author and at the NBAC web site (visited Jan. 14, 1998) <<http://www.nih.gov/nbac/minutes100496pm.htm>>).

cated that they, or a member of their family, had been refused health insurance on the basis of their genetic information.⁷⁴ The overwhelming majority of those surveyed felt that health insurers should not have access to genetic information.⁷⁵ A 1995 Harris poll of the general public found a similar level of concern.⁷⁶ Over 85% of those surveyed indicated they were very concerned or somewhat concerned that insurers or employers might have access to and use genetic information.⁷⁷

Discrimination in health insurance, and the fear of potential discrimination, threaten both society's ability to use new genetic technologies to improve human health and the ability to conduct the very research we need to understand, treat, and prevent genetic disease. To unravel the basis of complex disorders, scientists must analyze the DNA of many hundreds of people for each disease they study. Thus valid research on complex disorders will require the participation of large numbers of volunteers. But a pall of mistrust hangs over research programs because study volunteers are concerned that their genetic information will be used by insurers to discriminate against them.⁷⁸

There has been recent debate about how pervasive genetic discrimination actually is. Whether these fears are real or perceived, they clearly have had a negative impact on the ability of genetic researchers to find participants for their studies.⁷⁹ For example, "[i]n genetic testing studies at the NIH, nearly one third of eligible people offered a test for breast cancer risk decline to take it. The overwhelming majority of those who refuse, cite concerns about health insurance discrimination and loss of privacy as the reason."⁸⁰ There is little disa-

74. See E. Virginia Lapham et al., *Genetic Discrimination: Perspectives of Consumers*, 274 SCIENCE 621, 622 (1996).

75. See *id.*

76. See Sam Greengard, *Genetic Testing: Should you be afraid? It's No Joke*, 76 PERSONNEL J. 38 (1997) available in 1997 WL 12291208 (citing to a 1995 Harris Poll finding that 86% of 1000 respondents felt insurers may use genetic test results as a basis for decision-making).

77. See *id.*

78. See Geoffrey Cowley, *Flunk the Gene Test and Lose Your Insurance*, NEWSWEEK, Dec. 23, 1996, at 48.

79. Barbara L. Weber & Kathleen Calzone, Remarks at the Privacy Planning Meeting of NHGRI-NAPBC (June 9, 1997); see Dorothy Wertz, *How Many People Seek Genetic Testing for Cystic Fibrosis, BRCA1, and Huntington Disease?*, 1 GENE LETTER 1 (1997); Eliot Marshall, *Gene Tests Get Tested*, 275 SCIENCE 782 (1997).

80. See Francis S. Collins, Statement before the Congressional Task Force on Health Records and Genetic Privacy, *Preventing Genetic Discrimination in Health Insurance* (July 22, 1997) (transcript available with author and on the web site for the National Human Genome Research Institute at the National Institutes of Health (visited Feb. 6, 1998) <http://www.nhgri.nih.gov/Policy_and_public_affairs/Legislation/stearnsh.html>).

greement that there is a paucity of scientific data to address this issue and that obtaining accurate numbers will be difficult. It is important to realize, however, that while most people have not yet undergone genetic testing, with recent discoveries and a market increasingly driven by commercial interests, a rapid change in the near future is anticipated. Hopefully, it will not be necessary to wait until large numbers of individuals are injured by discrimination before legal and policy protections are put in place. Whether the incidence of discrimination is less than 1%, greater than 10%, or somewhere in between, efforts should be directed at preventing such misuse of genetic information based simply on the principle that unfair discrimination is wrong. Efforts to enact protective legislation must be based on principles and must not be deterred by debates over numbers and percentages.

The most substantial progress has been made in efforts to protect individuals from unfair discrimination in health insurance. The NIH-DOE ELSI Working Group and NAPBC jointly developed a series of recommendations for state and federal policy-makers which were published in 1995.⁸¹ These recommendations state that:

1. Insurance providers should be prohibited from using genetic information, or an individual's request for genetic services, to deny or limit any coverage or establish eligibility, continuation, enrollment, or contribution requirements.
2. Insurance providers should be prohibited from establishing differential rates or premium payments based on genetic information or an individual's request for genetic services.
3. Insurance providers should be prohibited from requesting or requiring collection or disclosure of genetic information.
4. Insurance providers and other holders of genetic information should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure would be made.⁸²

81. See Kathy L. Hudson et al., *Genetic Discrimination and Health Insurance: An Urgent Need for Reform*, 270 SCIENCE 391, 393 (1995).

82. See *id.*

The Health Insurance Portability and Accountability Act of 1996 (HIPAA)⁸³ was a landmark piece of federal legislation for genetics. The bill prohibits health insurers from using genetic information to deny or limit health insurance coverage to members of group plans.⁸⁴ However, it does not prohibit rate increases as a consequence of genetic test results, nor does it adequately protect individuals who are not in a group plan, thus leaving serious gaps in efforts to prevent genetic discrimination by insurance companies.⁸⁵ Since none of us can be assured that we will not need individual coverage in the future, and genetic information about us is permanent, the protections provided by HIPAA are not sufficient. A number of states have enacted legislation regarding genetic information and health insurance,⁸⁶ but as yet no fully comprehensive federal laws are in place.⁸⁷ There have been a number of additional pieces of federal legislation proposed during the 104th and 105th Congresses,⁸⁸ and the President of the United States announced his support for closing the remaining loopholes in July 1997.⁸⁹

In addition to the efforts put forth to address health insurance issues, the NIH-DOE ELSI Working Group and NAPBC also worked together to jointly develop a series of policy recommendations to prevent unfair discrimination in the workplace.⁹⁰ There are parallel recommendations aimed to prevent misuse of genetic information in both of these realms, but there is a possible difference in at least one respect in the context of the workplace.⁹¹ Because it is much more difficult to prove that a prospective or current employee was discriminated against based on genetic information, it is perhaps more critical

83. See Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191 110 Stat. 1936 (1996).

84. See *id.* § 9802(F).

85. See Jeffrey Fox, *Forget Washington: State Laws Threaten to Restrict Genetic Research, Too*, 9 J. NIH RESEARCH 19 (1997).

86. Karen H. Rothenberg, *Genetic Information and Health Insurance: State Legislative Approaches*, 23 J.L. MED. ETHICS 312, 312-19 (1995).

87. See Hudson et al., *supra* note 81, at 392.

88. See, e.g., H.R. 306, 105th Cong. (1997); H.R. 328, 105th Cong. (1997); S. 89, 105th Cong. (1997); S. 1600, 104th Cong. (1996); S. 1416, 104th Cong. (1995); H.R. 2690, 104th Cong. (1996). A comprehensive list of these proposed bills (including text, cosponsors and legislative history) can be found at the NHGRI web site (visited Jan. 14, 1998) <http://www.nhgri.nih.gov/Policy_and_public_affairs/Legislation/fedlegis.html#dlegis>.

89. President William Jefferson Clinton, Remarks at the Genetic Screening Event (July 14, 1997) (transcripts available at the 'White House Virtual Library' web site (visited Jan. 14, 1998) <<http://library.whitehouse.gov/>> by searching the "White House documents" site using the phrase "genetic" and the date "July 14, 1997").

90. See Karen Rothenberg et al., *Genetic Information and The Workplace: Legislative Approaches and Policy Changes*, 275 SCIENCE 1755, 1755-57 (1997).

91. See *id.* at 1756.

to incorporate limited *access* to this information by employers.⁹² Therefore, this effort requires stricter attention to privacy issues.⁹³

In 1997, recommendations for state and federal policy-makers regarding the prevention of misuse of genetic information in the workplace were published by the Hereditary Susceptibility Working Group of the NAPBC and the ELSI Working Group.⁹⁴ These recommendations are aimed at preventing the access and use of genetic information by employment organizations unless the information can be proven to be "job related and consistent with business necessity."⁹⁵ Currently, "[e]mployers in most jurisdictions are not prohibited from requiring genetic testing, even though there is insufficient evidence to justify the use of any existing test for genetic susceptibility⁹⁶ [with the possible exception of HLA testing of miners and machinists of beryllium]⁹⁷ as a basis for employment decisions."⁹⁸ "Employers may be reluctant to hire or promote individuals they believe will become prematurely unable to work."⁹⁹ Similar to the situation with health insurance, no comprehensive federal law addresses genetic discrimination in the workplace. However, "[i]n 1995, the Equal Employment Opportunity Commission (EEOC) issued a guidance in its compliance manual on the definition of 'disability' that addresses genetic discrimination in the workplace."¹⁰⁰ It stated that "the Americans with Disabilities Act (ADA) would 'protect individuals subjected to discrimination on the basis of genetic predisposition,' because in that situation the employer would be regarding the employee as disabled."¹⁰¹ In addition, a number of states have enacted laws that address the issue.¹⁰²

92. *See id.*

93. *See id.*

94. *See id.* at 1755.

95. *Id.* at 1756.

96. *Id.* at 1755.

97. *See* Luca Richeldi et al., *Interaction of Genetic and Exposure Factors in the Prevalence of Berylliosis*, 32 AM. J. INDUSTRIAL MED. 337, 338-40 (1997); *see* Luca Richeldi et al., *HLA-DPB1 Glutamate 69: A Genetic Marker of Beryllium Disease*, 262 SCIENCE 242, 242-44 (1993).

98. Rothenberg, *supra* note 90, at 1755.

99. Council on Ethical and Judicial Affairs, American Medical Association, *Use of Genetic Testing by Employers*, 266 JAMA 1827, 1827 (1991).

100. Rothenberg, *supra* note 90, at 1756 (citing EQUAL EMPLOYMENT OPPORTUNITY COMMISSION COMPLIANCE MANUAL, vol. 2, § 902, Order 915.002, 902-45 (1995) [hereinafter COMPLIANCE MANUAL]).

101. Rothenberg, *supra* note 90, at 1756 (quoting COMPLIANCE MANUAL, *supra* note 90 at 902-45).

102. *See* Rothenberg, *supra* note 90, at 1755-56. For example, Wisconsin and several other states have prohibited genetic testing of employees without informed consent, barred discrimination based on the results of genetic testing, and criminalized disclosure of test results without the employee's consent. *See id.* at 1755. New Jersey focuses more

The task of affording federal protection for the privacy of an individual's genetic information is perhaps the greatest challenge, given the inherent complexity of privacy legislation/regulation, in general, and the involvement of many more stakeholders than in the health insurance and employment anti-discrimination arena. The issue of privacy of genetic information is embedded in the larger context of medical records privacy, as most experts agree that any effort to separate the two will be intellectually impossible.¹⁰³ Federal law currently does not adequately protect the confidentiality of medical information.¹⁰⁴ "In fact, video rental records are afforded more federal protection than are medical records."¹⁰⁵ Language in HIPAA,¹⁰⁶ however, directed that progress must be made in the near future. The result of that directive was a report which was submitted to Congress last fall by the Department of Health and Human Services (HHS) Secretary Donna I. Shalala.¹⁰⁷ The report provided "recommendations for federal health record confidentiality legislation that would guarantee rights for patients and define responsibilities for record keepers, so that there will be clear guidance and real incentives for confidential, fair, and respectful treatment of personal health information, and penalties for its misuse."¹⁰⁸ Absent from these recommendations proposed by the HHS Secretary, however, was guidance for the protection of information generated or obtained in the course of research.

broadly on prohibiting the use of genetic information, including phenotype indicators and family history. *See id.* at 1756.

103. *See* NIH WORKING GROUP ON ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS OF HUMAN GENOME RESEARCH, GENETIC INFORMATION AND HEALTH INSURANCE 13 (NIH Publication No. 93-3686, 1993).

104. Federal law does protect "records relating to substance abuse or records in the custody of the federal government." Sheri Alpert, *Smart Cards, Smarter Policy: Medical Records, Privacy, and Health Care Reform*, 23 HASTINGS CENTER REP. 13 (1993). This paper also discusses the fact that some states recognize a provider-patient privilege and have specific laws to deal with highly sensitive medical information such as mental health records and/or AIDS test results. *See id.*

105. *Id.* at 13 (citing Pub. L. No. 100-618).

106. Health Insurance Portability and Accountability Act, Pub. L. No. 104-191, § 264, 110 Stat. 1936, 2033 (1996). This section on administrative simplification directed the Secretary of Health and Human Services (HHS) to promulgate regulations for "standards with respect to the privacy of individually identifiable health information" by August 21, 1997. *Id.*

107. *See* SECRETARY OF HEALTH AND HUMAN SERVICES, CONFIDENTIALITY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION 1997. The entire text of the report can also be found at the HHS web site (visited Feb. 6, 1998) <<http://aspe.os.hhs.gov/admsimp/pvcrec0.htm>>.

108. HHS Press Office, *Shalala Urges Congress to Protect Americans' Personal Medical Record* (visited Jan. 14, 1998) <<http://www.hhs.gov/news/press/1997pres/970911c.html>>.

Efforts at NHGRI have focused on the need for privacy and confidentiality safeguards in genetic research, as it has become increasingly clear that participation in such research has been negatively affected by fear of the loss of privacy of genetic information by potential participants. A background paper was drafted¹⁰⁹ and a workshop convened in September 1997 to bring together experts from a variety of disciplines. The goal was to assess current policies, ascertain varied viewpoints, stimulate dialogue between diverse and sometimes adversarial parties, and to identify areas where new or modified policies or practices might enhance privacy protection and promote the conduct of important biomedical research. It is expected that the outcome from that workshop will be the development and publication of a set of policy recommendations for researchers, research institutions, agencies, and/or Congress.

A. *The Future of Medicine*

Undoubtedly, the future will find predictive genetic testing available for a large number of disorders, including many with low penetrance. Patients will benefit from these test results in a number of significant ways. Information derived from these tests will allow individualized gene-based preventive medicine. Ultimately, the identification of the molecular basis of disease will allow for the development of gene-based therapies which have the potential to revolutionize the practice of medicine and save many lives. But a number of barriers threaten to limit the full medical benefit of the genetic revolution. It would be a serious mistake to assume that the only remaining barriers are technical and scientific ones, such as, improving mutation detection technologies or increasing the predictive accuracy of genetic testing for predisposing genes. The first barrier is the fear of discrimination as we have extensively discussed. Financial barriers are also of great concern. Commercial tests are expensive and the willingness of insurance companies to provide coverage is uncertain. Third, cultural barriers may exist. For example, the discrimination experienced by African-Americans as a result of sickle cell screening programs in the 1970's has had an understandably lasting effect on their willingness to embrace genetic testing.¹¹⁰ Similarly, the Ashkenazi

109. See Kathy Hudson et al., *Privacy and Confidentiality in Genetics Research*, 20 (1997) (unpublished draft on file with author).

110. See JAMES BOWMAN & ROBERT F. MURRAY, JR., *GENETIC VARIATION AND DISORDERS IN PEOPLES OF AFRICAN ORIGIN* 365-66 (1990); see also generally Patricia A. King, *The Past as Prologue: Race, Class, and Gene Discrimination in GENE MAPPING: USING LAW AND ETHICS AS GUIDES* 94 (George J. Annas & Sherman Elias eds., 1992).

Jewish population is very concerned that they may be subject to increased levels of discrimination and social stigmatization¹¹¹ due to the misinterpretation of recent genetic research studies.¹¹² Finally, educational barriers for medical and health professionals and the general public alike are potentially severe. Comprehending genetic information is rarely straightforward and demands knowledgeable medical and health professionals who thoroughly understand the appropriate use and limitations of genetic tests, and who can effectively translate this complex information to their patients. Our hope is that the future will see the general public conversant in the fundamental of principles of genetics and genetic disease. This would help to reduce the overwhelming quantity of information which most individuals now are forced to deal with for the first time during times of crisis - for example during prenatal testing or diagnosis of cancer. Incorporating a vocabulary of genetics into the vernacular will allow individuals to focus on the medical and psychosocial aspects of the information provided.

B. Use of Predictive Genetic Information in the Courts

The possible incorporation of predictive genetic information into decisions by the courts in cases, for example, of child custody, adoption, property disposition, and personal responsibility for criminal acts,¹¹³ is a disturbing prospect to scientists who never imagined such an application of this information. This troublesome scenario could be prevented before ever reaching juries. The recent unanimous Supreme Court decision in the case of *General Electric v. Joiner*¹¹⁴ bestowed upon trial judges great discretion to decide what type of scientific testimony can be presented to juries and was consistent with the *Daubert*¹¹⁵ rule which assigned judges the role of "gatekeepers."¹¹⁶ We welcome the exhortation by Justice Stephen G. Breyer in his concur-

111. See Sally Lehrman, *Jewish Leaders Seek Genetic Guidelines*, 389 NATURE 322 (1997); see also Rick Weiss, *Discovery of 'Jewish' Cancer Gene Raises Fears of More Than Disease*, WASH. POST, Sept. 3, 1997, at A3.

112. See Steven J. Laken et al., *Familial Colorectal Cancer in Ashkenazim Due to a Hypermutable Tract in APC*, 17 NATURE GENETICS 79 (1997); see also Jeffrey P. Struewing et al., *The Carrier Frequency of the BRCA1 185delAG Mutation Is Approximately 1 Percent in Ashkenazi Jewish Individuals*, 11 NATURE GENETICS 198 (1995).

113. Judge Rosalyn B. Bell, Remarks at the "NAPBC-NHGRI Workshop on Privacy and Confidentiality in Genetics Research" (Sept. 16, 1997); Judge Rosalyn B. Bell, Remarks at the University of Maryland School of Law workshop "Testing and Telling?: Implications for Genetic Privacy, Family Disclosure and the Law" (Oct. 8, 1997).

114. 118 S.Ct. 512 (1997).

115. *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993).

116. *Joiner*, 118 S.Ct. at 520.

ring opinion to encourage cooperation between the legal and scientific communities.¹¹⁷ The efforts of the Einstein Institute for Science, Health, and the Courts (EINSHAC)¹¹⁸ to develop a series of conferences for judges on cases involving genetics and molecular biology¹¹⁹ are an important step in the right direction toward improved communication and cooperation.

We believe that it would be a significant error to use an individual's or family's genetic sequence information in a legal context to confer either an advantage or disadvantage in such matters. The use of this information in the courts is likely to be misleading on two counts. The first is based on the scientific fact that in most cases, there will not be sufficient precision in the genetic information to justify basing crucial decisions on it. The increased risk figures that may be presented by various 'expert' witnesses will be based on population studies, yet the decisions to be made in the courtroom are about individuals. It would be highly unfortunate to have lawyers and judges making decisions based on uncertain predictive genetic information, or to ask juries to try to do so. After all, "research and discovery in the first century of the next millennium will reduce the uncertainties, but the nature of human variation is such that it will never be possible to have genetic tests that are perfect predictors of disease."¹²⁰

However, there is a second reason not to use an individual's or family's genetic sequence information in a legal context: to do so would be an unfair form of discrimination.¹²¹ People do not get to choose their own genes, nor can they change the genes they have been given. This is a civil rights issue as much as are race and gender discrimination. To base judgment on that which is inherited and immutable is simply wrong.

117. See generally Stephen Breyer, *The Interdependence of Science and Law*, 280 *SCIENCE* 537 (1998).

118. "EINSHAC is a non-profit corporation . . . [established] in 1993. . . . [It] is a research, technical assistance and education organization dedicated to assist courts manage scientific issues brought into complex litigation and prosecution." The Einstein Institute for Science, Health and the Courts, *The Courts and Science Online Magazine*, ¶ 1-2 (visited Apr. 8, 1998) <<http://www.ornl.gov/courts/journal1/describe.htm>>.

119. See Honorable Pauline Newman et al., *Genetics in the Courtroom: An Introduction*, 36 *JUDGES' J.* 1 (1997).

120. See PROMOTING SAFE AND EFFECTIVE GENETIC TESTING, *supra* note 21, at 3.

121. This is a proper response to the argument that the courts already base decisions on information that is less predictive than genetics.

III. SUMMATION

The link between a sequence alteration in the genome of an individual and the possibility of future disease is complex. However, the stakes are too high to allow the ethical discussions and legal debates to be held without demanding that they be based on a thorough understanding of the fundamental principles of genetics and the realities of what science can (and cannot) offer. Concepts such as locus heterogeneity, penetrance, and genotype-specific therapies must be well-grasped by all participants if the deliberations are to be meaningful particularly because these concepts are vital to understanding the scientific and medical value of the genetic information. The genetics research community will continue to work to educate lawyers, ethicists, policymakers, and others, and to ensure that an individual's genetic information is kept private and will be used solely for the medical benefit of the individual and society. The potential negative consequences of the misuse of genetic information and the depth of the impact it may have on the lives of individuals and their families demand our commitment to these efforts.