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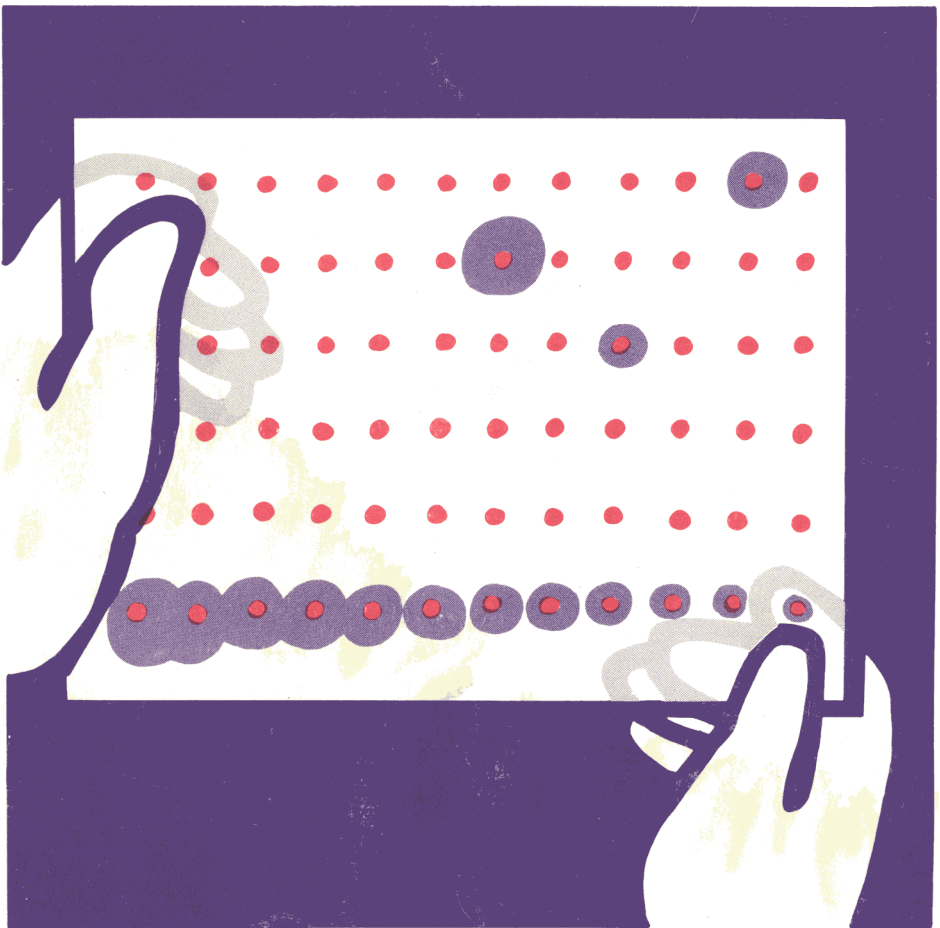
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# Screening and Counseling for Genetic Conditions

The Ethical, Social,  
and Legal Implications  
of Genetic Screening,  
Counseling, and  
Education Programs



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President's Commission for the Study of  
Ethical Problems in Medicine and  
Biomedical and Behavioral Research

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A Report on the Ethical,  
Social, and Legal Implications  
of Genetic Screening,  
Counseling, and Education  
Programs

February 1983

President's Commission for the Study of  
Ethical Problems in Medicine and  
Biomedical and Behavioral Research

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February 28, 1983

The President  
The White House  
Washington, D.C. 20500

Dear Mr. President:

On behalf of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, I am pleased to transmit our Report on Screening and Counseling for Genetic Conditions. This is one of several subjects that Public Law 95-622 directs the Commission to study and regarding which we are to report to the President, the Congress, and relevant Departments of government.

We have found that the capabilities of medical science to detect the existence of, or risk for, genetic disorders—though already impressive—will be greatly magnified in the coming decade. To illustrate the ethical as well as the scientific and logistical issues involved, we devote a chapter of the Report to examining the potential for screening for cystic fibrosis, the most prevalent lethal genetic disease in our country.

Genetic screening, when coupled with appropriate education and counseling, can provide people with information of enormous value. If this value is to be realized, it is important that those with responsibilities—in medical research and practice, in civic, religious, and voluntary organizations, and in the government at the local, state, and national levels—ensure that all activities in this field adhere to basic ethical norms of autonomy, privacy, equity, and beneficence. Although new Federal legislation is not specified among our recommendations, we do point to certain reforms in the law (involving adoption records, for example) that appear advisable to implement the principles set forth in this Report.

We are grateful to have had an opportunity to assist in developing public awareness and understanding of, and in improving public policy on, this important topic.

Respectfully,

A handwritten signature in dark ink, appearing to read "Morris B. Abram". The signature is fluid and cursive, written over a horizontal line.

Morris B. Abram  
Chairman

Enclosure





President's Commission for the Study of Ethical Problems  
in Medicine and Biomedical and Behavioral Research

Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

February 28, 1983

The Honorable George Bush  
President  
United States Senate  
Washington, D.C. 20510

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Morris B. Abram  
Chairman

Enclosure







President's Commission for the Study of Ethical Problems  
in Medicine and Biomedical and Behavioral Research

Suite 555, 2000 K Street, N.W., Washington, DC 20006 (202) 653-8051

February 28, 1983

The Honorable Thomas P. O'Neill, Jr.  
Speaker  
United States House of Representatives  
Washington, D.C. 20515

Dear Mr. Speaker:

On behalf of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, I am pleased to transmit our Report on Screening and Counseling for Genetic Conditions. This is one of several subjects that Public Law 95-622 directs the Commission to study and regarding which we are to report to the President, the Congress, and relevant Departments of government.

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Morris B. Abram  
Chairman

Enclosure



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# Introduction

The rapid advances now occurring in genetic screening techniques and the increased resources devoted to genetic counseling give Americans new opportunities to understand their biological heritage and to make their health care and reproductive plans accordingly. In this Report, the President's Commission responds to its legislative mandate to study the ethical and legal implications of these programs for genetic screening, counseling, and education.<sup>1</sup> On the whole, the Commission finds that advances in genetics have greatly enhanced health and well-being. Nevertheless, due regard for the subtle interplay of social norms and individual choices is required as genetic screening and counseling become increasingly important.

The new prominence of the human genetics field has already heightened public awareness of the significant issues that genetic procedures may soon raise for individual patients and their families, for health care providers, and for the public and its representatives.<sup>2</sup> In responding to the Congressional request, the Commission in this Report makes specific recommendations to guide those charged with designing and providing genetics programs, and reaches several general conclusions about the ethical issues at stake.

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<sup>1</sup> 42 U.S.C. §300v-1(a)(1)(C)(1981).

<sup>2</sup> See, e.g., Don Kaercher, *Genetic Diseases and Birth Defects: What Every Family Needs to Know*, BETTER HOMES AND GARDENS 66 (March 1980); Graham Chedd, *Who Shall Be Born?*, SCIENCE 81, 32 (Jan./Feb. 1981); Matt Clark, with Mariana Gosnell, *The New Gene Doctors*, NEWSWEEK 120 (May 18, 1981).



## The Report

**Scope of Screening Covered.** In genetic screening, an asymptomatic population is tested to identify people who may possess a particular genotype.<sup>3</sup> The term "screening" is often used to connote the initial step toward a definitive diagnosis, which then requires repeated or more precise testing of anyone identified as possibly having the condition. Sometimes, however, the term is used for more specific tests in individuals at risk for a condition when further analysis is not needed to yield a diagnosis or prognosis.<sup>4</sup>

Genetic testing often requires only a simple blood test and laboratory analysis. Some forms of screening, however, are performed on cells that have been grown in a laboratory. This is true of most diagnoses done during pregnancy, which usually involve analysis of cells found in a sample of amniotic fluid surrounding a fetus, although some prenatal diagnoses rely on examinations of the fetus by sonography, fetoscopy, or other techniques.

A number of the reasons screening is done are research-related. These include the testing of new genetic screening methods; attempts to establish a relationship between a particular genotype and a medical disorder or propensity; surveillance to detect the impact of environmental factors on genes (particularly on egg or sperm cells); and epidemiological studies of the frequency with which a gene or a chromosome abnormality occurs in a population. This Report does not explore the issues raised especially by screening for research purposes.

The possibility of screening to determine workers' susceptibility to disease from certain chemical factors in the workplace has received considerable attention from public and private groups. The U.S. Congress's Office of Technology Assessment is studying its potential uses and misuses, the Hastings Center is exploring its ethical implications, and some industries are examining its possible applications.<sup>5</sup> Because this issue is receiving extensive study already, the Commission decided not to address it at this time. Nevertheless, it is

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<sup>3</sup> For definitions of technical terms throughout this Report, see *Glossary*, Appendix A, pp. 105-08 *infra*; for further information on genetics and means of testing, see *Basic Concepts*, Appendix B, pp. 109-15 *infra*.

<sup>4</sup> See Committee for the Study of Inborn Errors of Metabolism, *GENETIC SCREENING: PROGRAMS, PRINCIPLES, AND RESEARCH*, National Academy of Sciences, Washington (1975) at 9-13.

<sup>5</sup> Office of Technology Assessment, *THE ROLE OF GENETIC TESTING IN THE PREVENTION OF OCCUPATIONAL ILLNESS*, U.S. Congress, Washington (forthcoming); Thomas H. Murray, *Statement before the Committee on Science and Technology, Subcommittee on Investigations and Oversight*, U.S. Congress, Oct. 6, 1982.

important not to separate these types of screening conceptually. The various reasons for screening and counseling or the settings in which they take place do not in themselves provide any basis for the adoption of different policies toward participants. Some of the Commission's conclusions will be equally relevant to the workplace.

The Commission has focused instead on genetic screening undertaken either to permit medical intervention (for example, through newborn screening) or to provide information about risks of genetic disease in natural-born children (through carrier screening or prenatal diagnosis). Both types sometimes occur as part of an individual provider-patient relationship, although screening is more frequently offered at a central genetics center (usually in a university medical center) under the auspices of a public health department or in conjunction with a community outreach effort such as a health fair or a special school, church, or synagogue program.

Genetic screening to uncover a person's need for medical care is similar to nongenetic screening (such as routine blood pressure or tuberculin tests) in that the goal is to determine whether remedial or preventive health care is needed. Whether a condition arises from a genetic or a nongenetic source is usually of less immediate consequence than the need for medical attention. Indeed, it may be difficult to draw a medical distinction between genetic and nongenetic conditions.<sup>6</sup> Genetic screening differs from other routine tests, however, in that the information produced is often relevant to medical decisions by individuals other than the person screened, even when this is not the primary reason for obtaining the information. For example, the discovery of a rare genetic defect in one person will usually lead physicians to suggest that the person's relatives also be screened.

Screening for reproductive reasons, on the other hand, is inherently genetic; information is sought primarily because of its impact on future generations. The difference between these two types of screening has important ethical and social consequences in certain cases. By revealing information about a person's genotype, screening undertaken to identify people in need of preventive or remedial treatment may, of course, raise questions of personal responsibility for ill health, along with feelings of guilt, because genes, unlike infectious or environmental causes of illness, are part of each individual's body. But these concerns are likely to be magnified when screening is done for reproductive reasons because the information provided—and the decisions based on it—have significance not only

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<sup>6</sup> Genetic predispositions are being found behind many conditions long thought of as nongenetic, while some genetic conditions are only regarded as "diseases" because of particular environmental settings or stimuli.

for people's own health, but also for the health of their children.

**Scope of Counseling Covered.** Genetic counseling helps people with a potential or manifest genetic problem understand and, if possible, adjust to genetic information; when necessary, it aids them in making decisions about what course to follow.<sup>7</sup> It is an individualized process in which a specialist in medical genetics confers with an individual, a couple, or sometimes a group seeking additional information or assistance. Before genetic screening tests enabled individuals to be tested prospectively, assessments of risks were based only on known genetic disease in the family. For example, following the birth of an affected child, the parents (and sometimes the extended family) might have sought genetic counseling. Since screening tests exist for only a very few genetic conditions, this retrospective counseling remains an important aspect of genetic counseling today.

For the most part, this Report considers counseling in conjunction with screening tests and programs. The demand for such counseling has grown dramatically in the past decades and promises to become increasingly important as new screening tests are developed. Nevertheless, the conclusions and recommendations in this Report are equally applicable to genetic counseling in other circumstances.

**Organization of the Study.** The Report is fairly brief for two reasons. First, it draws on other reports by the Commission that treat in more detail the subjects of informed consent and access to health care.<sup>8</sup> In those studies the Commission discusses the principles of well-being, self-determination, and equity and it therefore does not reiterate that analysis here. Second, the Report examines only those types of genetic screening and counseling that involve personal health risks and risks to any natural-born children. It leaves for the attention of others (and perhaps for future attention by the Commission) several forms of screening, such as tests for susceptibility or resistance to disease, that are beginning to attract researchers' attention.

The Report does look to the future, however, as it applies its findings about the ethical and legal implications of genetics programs to a frequently heralded genetic test for cystic

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<sup>7</sup> Ad Hoc Committee on Genetic Counseling, *Genetic Counseling*, 27 AM. J. HUMAN GENETICS 240-41 (1975).

<sup>8</sup> President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, MAKING HEALTH CARE DECISIONS, U.S. Government Printing Office, Washington (1982); President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, SECURING ACCESS TO HEALTH CARE, U.S. Government Printing Office, Washington (1983).

fibrosis. Research now under way is likely to lead to such a test in the near future. This condition is the most prevalent inherited lethal disorder in the United States. Among Caucasians, one person in 20 carries the gene for cystic fibrosis and one in every 1500-2000 infants is born with the disease.<sup>9</sup> If a test becomes available to identify these carriers, the demand for genetic screening and counseling could quickly become overwhelming.

To accommodate such an increase in an acceptable fashion, more than technical resources would be needed. Public understanding of the possible pitfalls of genetic testing as well as its potential benefits—of its human as well as its scientific implications—is essential if new screening capabilities are to yield safe, effective, equitable, and ultimately beneficial results.

The Commission hopes in this Report to further such public understanding. After sketching in Chapter One the basic facts about past genetic screening and counseling efforts, the Commission reaches a number of conclusions and recommendations in Chapter Two about how education, screening, and counseling programs should take account of important ethical and legal concerns. In Chapter Three, these points are applied to cystic fibrosis screening as a hypothetical test case; the issues that would be of concern there could also be expected to arise regarding tests developed for other genetic conditions.

The Commission held a hearing on this topic in May 1981 and discussed it at several other Commission meetings.<sup>10</sup> A partial draft of this Report was reviewed by the Commission with a panel of experts in March 1982; two months later, a revised draft was discussed, at which time the principal conclusions were approved by the Commissioners. On October 8, 1982, the Commission discussed and approved a revised draft, subject to editorial revisions.

## Summary of Conclusions and Recommendations

The Commission's basic conclusion is that programs to provide genetic education, screening, and counseling provide valuable services when they are established with concrete goals and specific procedural guidelines founded on sound ethical and legal principles. The major conclusions fall into five categories.

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<sup>9</sup> As explained in Appendix B, pp. 109-15 *infra*, it takes two genes to have the disease, one from each parent. The incidence of cystic fibrosis in other races is much lower.

<sup>10</sup> The participants in the Commission's study are set forth in *The Commission Process*, Appendix C, pp. 117-19 *infra*.

### **Confidentiality**

(1) Genetic information should not be given to unrelated third parties, such as insurers or employers, without the explicit and informed consent of the person screened or a surrogate for that person.

(2) Private and governmental agencies that use data banks for genetics-related information should require that stored information be coded whenever that is compatible with the purpose of the data bank.

(3) The requirements of confidentiality can be overridden and genetic information released to relatives (or their physicians) if and only if the following four conditions are met: (a) reasonable efforts to elicit voluntary consent to disclosure have failed; (b) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (c) the harm that identifiable individuals would suffer if the information is not disclosed would be serious; and (d) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.

- When it is known in advance that the results of a proposed screening program could be uniquely helpful in preventing serious harm to the biological relatives of individuals screened, it may be justifiable to make access to that program conditional upon prior agreement to disclose the results of the screening.

(4) Law reform bodies, working closely with professionals in medical genetics and organizations interested in adoption policies, should urge changes in adoption laws so that information about serious genetic risks can be conveyed to adoptees or their biological families. Genetic counselors should mediate the process by which adoptive records are unsealed and newly discovered health risks are communicated to affected parties.

### **Autonomy**

(5) Mandatory genetic screening programs are only justified when voluntary testing proves inadequate to prevent serious harm to the defenseless, such as children, that could be avoided were screening performed. The goals of “a healthy gene pool” or a reduction in health costs cannot justify compulsory genetic screening.

(6) Genetic screening and counseling are medical procedures that may be chosen by an individual who desires information as an aid in making personal medical and reproductive choices.

- Professionals should generally promote and protect patient choices to undergo genetic screening and

counseling, although the use of amniocentesis for sex selection should be discouraged.

- The value of the information provided by genetic screening and counseling would be diminished if available reproductive choices were to be restricted. (This is a factual conclusion that is not intended to involve the Commission in the national debate over abortion).

### **Knowledge**

(7) Decisions regarding the release of incidental findings (such as nonpaternity) or sensitive findings (such as diagnosis of an XY-female) should begin with a presumption in favor of disclosure, while still protecting a client's other interests, as determined on an individual basis. In the case of nonpaternity, accurate information about the risk of the mother and putative father bearing an affected child should be provided even when full disclosure is not made.

(8) Efforts to develop genetics curricula for elementary, secondary, and college settings and to work with educators to incorporate appropriate materials into the classroom are commendable and should be furthered. The knowledge imparted is not only important in itself but also promotes values of personal autonomy and informed public participation.

(9) Organizations such as the Association of American Medical Colleges, the American Medical Association, and the American Nursing Association should encourage the upgrading of genetics curricula for professional students. Professional educators, working with specialty societies and program planners, should identify effective methods to educate professionals about new screening tests. Programs to train health professionals, pastoral counselors, and others in the technical, social, and ethical aspects of genetic screening deserve support.

### **Well-Being**

(10) A genetic history and, when appropriate, genetic screening should be required of men donating sperm for artificial insemination; professional medical associations should take the lead in identifying what genetic information should be obtained and in establishing criteria for excluding a potential donor.

- Records of sperm donors are necessary, but should be maintained in a way that preserves confidentiality to the greatest extent possible.
- Women undergoing artificial insemination should be given genetic information about the donor as part of the informed consent process

(11) Screening programs should not be undertaken unless the results that are produced routinely can be relied upon.

- Screening programs should not be implemented until the test has first demonstrated its value in well-conducted, large-scale pilot studies.
- Government agencies involved in introducing new screening projects should require appropriate pilot studies as a prerequisite to approval of the product or to the funding of services.
- Government regulators, funding organizations, private industry, and medical researchers should meet to discuss their respective roles in ensuring that a prospective test is studied adequately before genetic screening programs are introduced.

(12) A full range of prescreening and follow-up services for the population to be screened should be available before a program is introduced.

- Community leaders and local organizations should play an integral part in planning community-based screening programs.
- State governments should consider establishing a review group with professional and public members to oversee genetic services.
- New screening programs should include an evaluation component.

### **Equity**

(13) Access to screening may take account of the incidence of genetic disease in various racial or ethnic groups within the population without violating principles of equity, justice, and fairness.

(14) When a genetic screening test has moved from a research to a service delivery setting, a process should exist for reviewing implicit or explicit policies that limit access to the genetic service; the review should be responsive to the full range of relevant considerations, to changes in relevant facts over time, and to the needs of any groups excluded.

- The time has come for such a review of the common medical practice of limiting amniocentesis for “advanced maternal age” to women 35 years or older.

(15) Determination of such issues as which groups are at high enough risk for screening or at what point the predictive value of a test is sufficiently high require ethical as well as technical analyses.

(16) Cost-benefit analysis can make a useful contribution to allocational decisionmaking, provided that the significant limitations of the method are clearly understood; it does not provide a means of avoiding difficult ethical judgments.

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# The Evolution and Status of Genetic Services

# 1

A gene is one of those things that would have had to be invented if it had not already existed—indeed, genes were “invented” before they were discovered. It had long been observed that all living things largely resemble their parents, but it was not until the last century that systematic attention was paid to the way plant and animal characteristics varied from one generation to the next. Gregor Mendel, the father of modern genetics, spoke of “inheritance factors” through which such variations pass from one generation to the next. Later, the Greek word *gene*<sup>1</sup> (meaning born, or produced) was chosen to designate these units of heredity. As the study of genetics moved from plants and lower animals to humans, the patterns of inherited human genetic conditions were observed and it became possible to tell people of the chances that particular diseases would occur in themselves or their children. Today scientists understand a great deal about the composition of genes and can even isolate particular genes of interest.<sup>2</sup>

## The Roots of Medical Genetics

Although genetics as a formal discipline emerged after the rediscovery in 1900 of Mendel’s nineteenth-century experiments, genetic diseases had been described in the scientific literature long before then. Even without an understanding of

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<sup>1</sup> Many of the technical and medical terms used throughout this Report are defined in the *Glossary*, Appendix A, pp. 105-08 *infra*.

<sup>2</sup> The newly acquired ability to splice genes and manipulate genetic material is the subject of another Commission Report, *SPLICING LIFE*, U.S. Government Printing Office, Washington (1982). Although these techniques are sometimes used to diagnose genetic conditions, the technology of gene splicing is not specifically addressed in this Report.



the basic genetic mechanisms, physicians had to care for and advise individuals suffering from diseases that “run in the family.” During the early years of this century, informal sources of information (“old wives’ tales”) gave way to the new science of genetics, which led to more formal genetic counseling sessions.

**The Development of Genetic Counseling.** The first American genetic counseling center was probably the Eugenic Records Office in Cold Spring Harbor, New York, founded by Dr. Charles B. Davenport in 1915 at the height of the American eugenics movement.<sup>3</sup> The term eugenics refers to efforts to improve the inborn characteristics of the human species by applying rules of heredity to human propagation. In the first part of this century many eugenicists called for regulated marriages, sterilization, immigration restrictions, and permanent confinement of individuals considered “misfits.”

From its association with the eugenics movement, genetic counseling fell out of favor beginning in the 1930s, as the role of the environment in human behavior became better understood and as people recoiled from Hitler’s racist use of eugenics. Many tenets of eugenics rested upon genetic principles that were not well established or fully understood and their application was seen as contrary to the American system’s protection of basic civil liberties.<sup>4</sup>

The study of genetics became predominantly an academic pursuit for the next 20 years. Informal counseling was done, however, by academicians who were primarily involved in basic genetic research rather than clinical medicine. The early eugenicists’ misuse of genetic information did leave a legacy for the newly emerging field of human genetics: wariness over the abuses of genetics led to an emphasis on “nondirective” counseling, an uncharacteristic attitude among health care professionals.<sup>5</sup>

By the 1960s great strides had been made in understanding human genetics. The new information gave counselors a broader and more scientific basis for telling families about the recurrence risks and inheritance patterns of an increasing number of diseases. The development of genetic tests based on blood and cell samples introduced the field of prospective counseling and helped shift counseling from primarily nonmedical settings to screening programs involving public health officials, physicians, nurses, and other health professionals, often working in specialized genetics centers in hospitals and

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<sup>3</sup> *Editorial Comment: Eugenics Quarterly Succeeds Eugenical News*, 1 EUGENICS QUARTERLY (March 1, 1954).

<sup>4</sup> See, e.g., Kenneth M. Ludmerer, *GENETICS AND AMERICAN SOCIETY: A HISTORICAL APPRAISAL*, Johns Hopkins Univ. Press, Baltimore (1972).

<sup>5</sup> See pp. 37-38 *infra*.

universities. Thirty years ago there were only a handful of “centers” with any specialized expertise in the field; today there are a total of about 500 centers and satellite facilities in the United States.<sup>6</sup>

**The Development of Genetic Screening.** The renewal of physicians’ interest in genetic diagnosis was sparked in 1959 by an explanation of chromosomal disorders that laid the basis for understanding a wider range of inherited conditions.<sup>7</sup> In the 1960s the potential contribution of medical genetics to health became clearer; progress in biochemical and molecular genetics made screening possible and focused attention on genetic diseases. By the end of the decade medical geneticists took screening one step further by introducing diagnosis of chromosomal and metabolic disorders before birth.<sup>8</sup>

Yet despite this great expansion in knowledge, genetics is only beginning to play a significant part in health care. Before the end of the century, however, genetic screening and counseling are certain to become major components in both public health and individual medical care. Although it is not imminent, the time can already be envisioned when virtually all relevant information about a person’s genotype—including all his or her “abnormal” genes and chromosomes—will be readily accessible. Whether such personal details remain as arcane and little-understood to the general public as, for example, fingerprints are today or whether—in contrast to present attitudes toward medical information—they become as public as a person’s name or appearance or as vital as information about infectious disease will depend upon the complex interaction of many cultural, political, and scientific factors.

## Genetic Screening Capabilities

Since the 1950s three major categories of genetic screening have been developed. Screening of newborns is aimed at detecting in early infancy serious genetic diseases for which early therapeutic intervention can avert serious health consequences or even death. Carrier screening identifies individuals whose genetic makeup includes a gene or a chromosome abnormality that may be harmful for their offspring or occa-

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<sup>6</sup> National Clearinghouse for Human Genetic Diseases, *CLINICAL GENETIC SERVICE CENTERS: A NATIONAL LISTING*, Dept. of Health and Human Services, Washington (1980).

<sup>7</sup> J. Lejeune, M. Gautier, and R. Turpin, *Etude des Chromosomes Somatiques de Neuf Enfants Mongoliens*, 248 CR ACAD SCI. (Paris) 1721 (1959); C.E. Ford *et al.*, *The Chromosomes in a Patient Showing Both Mongolism and the Klinefelter Syndrome*, 1 LANCET 709 (1959).

<sup>8</sup> C.B. Jacobson and R.H. Barter, *Intrauterine Diagnosis and Management of Genetic Defects*, 99 AM. J. OBSTET. GYNECOL. 796 (1967).

sionally even for themselves (even though they have not yet had any symptoms of the condition). For recessive diseases, a person identified as a carrier usually need be concerned that the disorder might occur in offspring only if his or her mate carries the same abnormal gene. Prenatal screening yields information before birth about the presence of genetic disease through examinations of a fetus, of cells it has shed into the amniotic fluid, or of its blood, including blood cells that cross the placenta into the maternal bloodstream.

### **Newborn Testing**

**Metabolic tests.** Genetic screening began in the early 1960s with tests for “inborn errors of metabolism,” conditions that involve an abnormal or missing enzyme or other protein as a result of a defective gene, usually inherited on a recessive basis. Normal human functioning depends upon the coordinated activities of many enzymes and other proteins necessary for proper cellular activity and structure. Thus, a mutation that results in the absence or abnormality of an enzyme or other protein interrupts this coordination and can lead to a metabolic disorder. Inborn errors of metabolism include phenylketonuria (PKU), Tay-Sachs disease, and sickle-cell anemia. Although some inborn errors are untreatable and even lethal, others can now be treated by supplying the missing substance or by removing something harmful from the affected person’s environment. In some cases, early intervention is crucial to avoid premature death or the occurrence of serious and irreversible complications. Consequently, efforts to identify such metabolic disorders in newborns have been a major focus of genetic screening.

The inborn errors of metabolism that are the targets of newborn screening are inherited on an autosomal recessive basis, meaning there is a 25% risk that any subsequent pregnancy will result in a child with the same condition.<sup>9</sup> Newborn screening can also therefore identify couples who might benefit from genetic counseling and possibly prenatal diagnosis of any future pregnancies.

**Phenylketonuria.** Newborns were the first subjects of mass genetic screening in the United States. In 1961, Dr. Robert Guthrie developed a simple test for PKU,<sup>10</sup> a relatively rare autosomal recessive disease (see Table 1). In PKU an enzyme deficiency prevents the proper breakdown of an amino acid—phenylalanine—that is essential for health. This “error” in metabolism produces severe mental retardation and other physical anomalies. If a PKU infant is placed on a diet low in

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<sup>9</sup> For an explanation of inheritance patterns and other basic concepts in genetics, see Appendix B, pp. 109-15 *infra*.

<sup>10</sup> Robert Guthrie, *Blood Screening for Phenylketonuria* (Letter), 178 J.A.M.A. 863 (1961).

**Table 1:****Incidence and Carrier Frequency of Selected Genetic Conditions**

Sources: *Committee for the Study of Inborn Errors of Metabolism, GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH, National Academy of Sciences, Washington (1975); Cystic Fibrosis Foundation and the National Institutes of Health, Research Highlights, 1982-83, mimeo., Washington (1982).*

Condition	Disease Incidence	Carrier Frequency
Sickle-Cell Anemia*	1 in 400-600 American Blacks	1 in 10-12 American Blacks
Cystic Fibrosis	1 in 1600-2500 Caucasians	1 in 20-25 Caucasians
Tay-Sachs Disease	1 in 3600 Ashkenazi Jews	1 in 30 Ashkenazi Jews
Phenylketonuria	1 in 14,000 of the general population	1 in 60 of the general population

\* In addition to those of African heritage, individuals of Greek and Italian background are also at increased risk.

phenylalanine, however, the retardation and other clinical manifestations of PKU can be avoided.

In the test developed by Dr. Guthrie, a drop of blood taken by pricking a newborn's heel (a relatively painless and risk-free procedure) is absorbed by a piece of filter paper and the level of phenylalanine in the infant's blood is determined by analysis of that sample. The process is now so automated that many samples can be tested at one time.

In 1962, Massachusetts tried a voluntary screening program for PKU using an early version of the Guthrie test. The program, operated through the state-run laboratory, demonstrated the feasibility of mass genetic screening and elicited wide cooperation among physicians and hospitals. The discovery of three "positives" for PKU in the first 8000 tests stimulated interest. The following year, at the urging of groups working on behalf of retarded children and with the support of officials of the state health department, Massachusetts adopted the first U.S. mandatory PKU screening law.<sup>11</sup>

The National Association for Retarded Children (NARC) conducted an extensive grass-roots lobbying effort during the 1960s to establish mandatory PKU screening legislation. Organized medicine, although often critical of legislative interven-

<sup>11</sup> Mass. Gen. Laws Ann. Ch. III § 110 A (West) 1963.

tions in health care, largely left the field to NARC and its medical allies or put up only limited opposition. Most legislators apparently regarded PKU screening as a way to prevent mental retardation and not as a uniquely “genetic” program. Indeed, the range of genetic variation in the gene responsible for PKU was not then fully understood even by NARC and its medical consultants. Many conditions that gave test results similar to PKU stemmed from different genetic variants; this became apparent only after further experience with screening and treating children.<sup>12</sup> Nonetheless, legislation making PKU screening compulsory was swiftly adopted across the country; 43 states had such statutes by 1973.<sup>13</sup>

These laws were adopted despite a number of problems and questions uncovered in field trials of the tests, some of which remain unresolved today. In 1967, the Technical Committee on Clinical Programs for Mentally Retarded Children of the U.S. Children’s Bureau funded a collaborative study to address these questions. The project has gathered data useful in assessing the effectiveness of dietary therapy, and many of the initial questions have been answered.<sup>14</sup> Although some of these issues ought to have been laid to rest before mandatory screening was initiated, newborn PKU screening today represents what many consider an ideal preventive health measure.

Nonetheless, some concerns remain. Foremost among these is the fact that babies are usually tested just before going home from the hospital, which in the United States today tends to be within three days of their birth, which makes an accurate diagnosis difficult. At this time many newborns (especially those who are breast-fed) have not taken in enough protein to raise their phenylalanine levels, which can increase the rate of undetected cases during the initial screen (the so-called false negatives). In an attempt to reduce the rate of false negatives, the cut-off point above which the phenylalanine level is regarded as “positive” is set at a low level. Yet this results in a high rate of “false positives.” Indeed, more than 90% of the initial positive results during mass screening are found on further testing not to be cases of PKU. Thus thorough follow-up testing remains imperative to avoid inappropriate diagnoses.

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<sup>12</sup> J.S. Yu *et al.*, *Atypical Phenylketonuria, an Approach to Diagnosis and Management*, 45 ARCH. DIS. CHILD. 561 (1970); S. Berlow, *Progress in Phenylketonuria, Defect in the Metabolism of Biopterin*, 65 PEDIATRICS 837 (1980).

<sup>13</sup> For a summary of each state statute, see Committee for the Study of Inborn Errors of Metabolism, *GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH*, National Academy of Sciences, Washington (1975) at 56-69.

<sup>14</sup> M.L. Williamson *et al.*, *Correlates of Intelligence Test Results in Treated Phenylketonuric Children*, 68 PEDIATRICS 2 (1981).

Follow-up testing had been urged as a routine procedure at the first visit to the pediatrician or clinic for any baby whose PKU test was done when he or she was only a few days old because of concern about the rate of false negatives of such early tests.<sup>15</sup> The American Academy of Pediatrics' Committee on Genetics recently reviewed and revised this recommendation. Rescreening is now recommended only for all infants initially screened during their first 24 hours of life.<sup>16</sup> As several geneticists who testified before the Commission pointed out, mandatory screening makes little sense unless follow-up services, in the form of further diagnostic tests and dietary treatment, are also provided.

Some newly recognized long-term implications of PKU testing require additional attention.<sup>17</sup> Very high rates of mental retardation and other birth defects have been reported in the children of women who were diagnosed in the newborn period as having PKU.<sup>18</sup> These women, who did not become mentally retarded because they began dietary therapy at a very early age, were taken off the special diet between the ages of seven and ten, by which time the risk to their own mental development had decreased markedly. Studies are now being undertaken to see whether the damage to their children can be prevented if the women return to the low-phenylalanine diet during pregnancy. Since some damage may occur very early in gestation, before a woman is aware she is pregnant, women who have been treated for PKU in childhood may have to return to the diet throughout their childbearing years if they wish to avoid the risk of damaged children. Or they may wish to avoid having children at all. At the very least, long-term follow-up and counseling of women treated for PKU when they were growing up is now considered a necessary extension of increased diagnosis and treatment of this disease.

Other metabolic defects. Relatively simple and inexpensive tests that can be done on one blood specimen from a newborn have been developed for a variety of other "metabolic errors," and many states have incorporated the additional tests into their screening programs. In New York, for example, newborn screening is mandated not only for PKU, sickle-cell anemia, and congenital hypothyroidism but also for several

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<sup>15</sup> N.A. Holtzman, E.D. Mellits, and C.H. Kallman, *Neonatal Screening for Phenylketonuria: II. Age Dependence of Initial Phenylalanine in Infants with PKU*, 53 PEDIATRICS 3 (1973).

<sup>16</sup> Committee on Genetics, *New Issues in Newborn Screening for Phenylketonuria and Congenital Hypothyroidism*, 69 PEDIATRICS 1 (1982).

<sup>17</sup> L. Carter *et al.*, *Prevention of Mental Retardation in Offspring of Hyperphenylalaninemic Mothers*, 72 AM. J. PUB. HEALTH 1386 (1982).

<sup>18</sup> R.R. Lenke and H.L. Levy, *Maternal Phenylketonuria and Hyperphenylalaninemia*, 303 NEW ENG. J. MED. 1202 (1980).

very rare conditions including maple syrup urine disease, homocystinuria, histidinemia, galactosemia, and adenosine deaminase deficiency.<sup>19</sup>

For some disorders (such as congenital hypothyroidism) early treatment, dietary or otherwise, can clearly prevent the clinical expression of the disease or improve the long-term prognosis. For others, however, the benefits of early detection are either unclear (for example, in sickle-cell anemia) or unknown (histidinemia). And in some cases, such as maple syrup urine disease, screening presents especially difficult ethical dilemmas since early diagnosis followed by costly treatment may only delay an inevitable death by a few, very burdened years.<sup>20</sup> Although statewide newborn screening programs have provided a great deal of data that has been useful in evaluating the genetic, biochemical, and clinical characteristics of metabolic disorders, for at least some conditions some families may prefer not to receive the information.

**Chromosome tests.** Advances in cytogenetic techniques have also made chromosomal screening possible. Chromosomal surveys of all the live births at several medical centers were done in the late 1960s to find the occurrence of several chromosome variations in humans. There is some evidence that as many as one in 200 newborns might have some type of chromosomal anomaly.<sup>21</sup> Although these studies yielded valuable information for research purposes, they also raised a number of ethical and legal concerns, particularly with regard to sex chromosome aneuploides.

One anomaly in sex chromosomes in particular—the XYY pattern—attracted particular public attention during the 1960s and 1970s. Chromosome screening done in a number of prisons and maximum security hospitals revealed a higher frequency of men with an extra Y chromosome than would be expected based upon the then-existing data on the occurrence of the anomaly among adult males generally.<sup>22</sup> To study any possible connection between the XYY genotype and antisocial behavior, scientists believed that more reliable figures on the rate of

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<sup>19</sup> N.Y. Pub. Health Law § 2500(a) (McKinney 1977).

<sup>20</sup> N.A. Holtzman, C.O. Leonard, and M.R. Farfel, *Issues in Antenatal and Neonatal Screening and Surveillance for Hereditary and Congenital Disorders*, 2 ANN. REV. PUB. HEALTH 219 (1981).

<sup>21</sup> Ernest B. Hook and John L. Hamerton, *The Frequency of Chromosomal Abnormalities Detected in Consecutive Newborn Studies*, in E.B. Hook and I.H. Porter, eds., *POPULATION CYTOGENETICS: STUDIES IN HUMANS*, Academic Press, New York (1977) at 63.

<sup>22</sup> See, e.g., P.A. Jacobs *et al.*, *Aggressive Behavior, Mental Subnormality and the XYY Male*, 208 NATURE 1351 (1965); *What is to be Done With the XYY Fetus?* (Editorial), 1 BRIT. MED. J. 1519 (1979); Richard F. Daly and J. Preston Harley, *Frequency of XYY Males in Wisconsin State Correctional Institutions*, 18 CLINICAL GENETICS 116 (1980).

XYYs in the general population were needed; the most accurate measure, they concluded, would be the frequency of XYY in newborns. Plans were also made to follow the development of selected groups of XY and XYY children from birth onwards.

When it was learned that researchers at Harvard had proposed such a study, strong opposition was voiced from some quarters because all the facts had not been revealed to the families, the subjects were said to be at risk of a "self-fulfilling prophecy" of deviance, and the research was thought by some to divert attention from the more important (and more remediable) environmental causes of behavioral problems.<sup>23</sup> That study was called off, but others proceeded and have yielded important information about the effects of sex chromosome aneuploides and about the concern that informing parents about the condition would be deleterious.<sup>24</sup> A recent report of one such study of children with various sex chromosome abnormalities concluded that "diagnosis of sex chromosome aberrations at birth or during early childhood with full information and guidance to parents and educators are of great importance for the development of the children, especially concerning learning and behavior."<sup>25</sup>

**Carrier Screening.** Whereas newborn screening is aimed primarily at discovering children who might benefit if their diseases are treated before the symptoms develop, carrier screening is intended primarily to provide people of reproductive age with information of relevance not to their own health but to that of any children they might have. Carrier screening of selected populations began in the United States in the early 1970s with two genetic disorders: sickle-cell anemia and Tay-Sachs disease. The accurate and simple tests that had been developed could be applied on a mass scale at a relatively modest per-unit cost. These diseases, rare in the general

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<sup>23</sup> A useful treatment of the issue can be found in Alan M. Dershowitz, *Karyotype Predictability and Culpability*, and E.B. Hook, *Geneticophobia and the Implications of Screening for the XYY Genotype in Newborn Infants*, and in the discussion that follows in A. Milunsky and G. Annas, eds., *GENETICS AND THE LAW*, Plenum Press, New York (1976) at 63, 73, 87.

<sup>24</sup> K. Tennes *et al.*, *A Developmental Study of Girls With Trisomy X*, 27 AM. J. HUM. GENETICS 71 (1975); J. Nielsen, A.M. Sorensen, and K. Sorensen, *Mental Development of Unselected Children with Sex Chromosome Abnormalities*, 59 HUM. GENETICS 324 (1981); M.M. Puck, *Some Considerations Bearing on the Doctrine of Self-Fulfilling Prophecy in Sex Chromosome Aneuploidy*, 9 AM. J. MED. GENETICS 129 (1981).

<sup>25</sup> Nielsen, Sorensen, and Sorensen, *supra* note 24, at 324. For further discussion of disclosing information on sex chromosome abnormalities, see pp. 62-63 *infra*.



population, occur in well-defined populations at much higher frequencies (see Table 1, p. 13).

Since some of the conditions create severe economic as well as personal burdens, the higher frequency in certain segments of the population is great enough to make detection of carriers cost-effective. The hope was that some serious [and often incurable] diseases could be prevented by counseling those people found through screening to be at increased risk of having affected children. Screening carriers who were not themselves at risk for a disease was a new concept in preventive health care, and focused a great deal of attention on the areas of bioethics and the law because of a number of unanticipated developments.

Heterozygous carriers of recessive disorders are usually asymptomatic; previously, such people became aware of their variant gene only through the birth of an affected child. Although each person carries about six or seven deleterious genes, most of these genes are extremely rare; the chance of the same one occurring in a person's mate is therefore very small for most recessive disorders. (The likelihood of these disorders occurring in isolated, inbred populations is obviously much greater because these people have many more genes in common.)

Carrier screening offers a way to detect heterozygotes for recessive disorders prior to a couple producing a child with a genetic defect. Moreover, if a child is born with a genetic defect, carrier screening can be used by the child's relatives to learn whether they risk having children with the same genetic problem.

**Tay-Sachs.** In 1970, a pilot screening program for Tay-Sachs carriers among members of the Jewish communities in the Baltimore-Washington area signaled the beginning of large-scale carrier screening in the United States.<sup>26</sup> The underlying metabolic defect in Tay-Sachs disease was discovered in 1969; the gene that is normally responsible for the production of the enzyme hexosaminidase A (Hex-A) does not function properly. A total lack of Hex-A activity, as observed in Tay-Sachs disease, prevents the breakdown of certain fatty substances found in the brain. The accumulation of these substances leads to severe neurologic problems and to death by the age of two to four, despite intensive medical and nursing support. When tested, individuals who carry one Tay-Sachs gene exhibit decreased but sufficient Hex-A activity: homozygous individu-

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<sup>26</sup> Michael M. Kaback and R.S. Zeiger, *The John F. Kennedy Institute Tay-Sachs Program: Practical and Ethical Issues in an Adult Genetic Screening Program* in B. Hilton et al., eds., *ETHICAL ISSUES IN HUMAN GENETICS: GENETICS COUNSELING AND THE USE OF GENETIC KNOWLEDGE*, Plenum Press, New York (1973) at 131.

als, who have two copies of the Tay-Sachs gene, show no Hex-A activity.

With the understanding of the underlying defect, screening for Tay-Sachs disease became possible. A combination of factors contributed to the generally accepted success of Tay-Sachs screening in this country.<sup>27</sup>

- (1) Tay-Sachs disease occurs predominantly in a well-defined population.
- (2) The disease is characterized by a drawn-out process of progressive degeneration and dying, and is incurable.
- (3) A simple, accurate, and relatively inexpensive test can detect a Tay-Sachs carrier through blood samples; although somewhat more complex, a test can also be performed to determine if a pregnant woman who was not screened prior to conceiving a child is a Tay-Sachs carrier.
- (4) Tay-Sachs disease can be detected prenatally.
- (5) The first pilot test was preceded by careful planning, including the active involvement of community leaders and institutions.

This involvement of the community proved to be of utmost importance in the success of carrier screening programs. Fourteen months of planning, leadership training, personnel development, and public education preceded the Baltimore-Washington pilot program. Community-based involvement and cooperation were encouraged, and trained volunteers and media coverage played a major role in the education effort; indeed, peer pressure and community sources of information (such as synagogue groups) appear to have been more influential than physicians in getting people to be screened. In addition, the program was aimed at married people of child-bearing age, a highly motivated population. As a result of these efforts, screening was voluntarily sought by a very high percentage of the high-risk population.

Following the success of the pilot program, screening for Tay-Sachs spread rapidly. By June 1981, a total of 350,000 young Jewish adults had been screened voluntarily in 102 centers throughout the world. The screening detected 337 carrier-couples, for whom a total of 912 pregnancies were monitored prenatally; 202 fetuses were found to have Tay-Sachs. A total of 13 children were born with Tay-Sachs disease in North America in 1980.<sup>28</sup> (Prior to 1970, between 50 and 100 such children were born per year.) Until cures and better

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<sup>27</sup> *Id.*

<sup>28</sup> Michael M. Kaback, *Tay-Sachs Disease: A Model for Genetic Disease Control*, at Arnold O. Beckman Conference in Clinical Chemistry, Monterey, Calif., Oct. 12, 1981.

therapies are available for genetic diseases such as Tay-Sachs, carrier screening and prenatal diagnosis will be an “important, though imperfect, alternative approach,” as the physician who pioneered screening recently commented.<sup>29</sup>

The success of the carrier screening program can also be traced to the availability of prenatal screening, which has provided carrier couples with an option that did not exist previously. In the past, couples who had a child with Tay-Sachs disease often found the 25% risk of having another affected child to be unacceptable, and decided therefore not to have any more children. Prenatal screening for Tay-Sachs has meant the continuation of countless pregnancies and the conception of hundreds of infants who would otherwise not have been born.<sup>30</sup> This is true both of couples who have one affected child and of those who discovered their carrier status through the genetic screening test. Physicians now make more referrals for screening because of increased awareness of the test—awareness that has been sharpened by a number of malpractice suits against physicians who failed to inform patients at risk for genetic conditions about available screening tests.

**Hemoglobin disorders.** The history of screening for the hemoglobinopathies (the diseases affecting the oxygen-carrying capacity of red blood cells) tells a different tale because of technical as well as cultural factors.<sup>31</sup> In the United States, popular attention focused on sickle-cell anemia, particularly in the black community, although recent efforts have also been directed to beta-thalassemia, a related hemoglobin disorder sometimes called Cooley’s anemia.

An estimated 8-10% of the American population of African ancestry are sickle-cell heterozygotes (see Table 1, p. 13); the carrier frequency is also high among people who originated in other areas (such as the Mediterranean basin) where falciparum malaria is endemic. This high rate of occurrence of a condition that is usually lethal in its homozygous form is apparently due to the greater resistance that sickle-cell heterozygotes have to the effects of falciparum malaria. This “heterozygote advantage” means that carriers of the gene are more likely to survive to adulthood and therefore to pass their genes along to the next generation.

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<sup>29</sup> Michael M. Kaback, in *Genetic Testing Imperfect But is Still Valuable*, OB-GYN NEWS, Feb. 15-28, 1982, at 1.

<sup>30</sup> *Id.*

<sup>31</sup> GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH, *supra* note 13, at 116-33.

In the early 1970s media attention in the United States focused on sickle-cell anemia as a "neglected disease."<sup>32</sup> Remedying this neglect became a prime political objective in the black community. Seizing upon the newly developed screening tests, programs were launched not only by physicians but by community groups; in a few states, laws were even passed requiring sickle-cell tests for newborns, school-children, marriage license applicants, and inmates of penal institutions.<sup>33</sup> The National Sickle Cell Anemia Control Act, enacted in 1972, helped reverse the movement toward mandatory laws by limiting the use of Federal funds to voluntary carrier screening programs.<sup>34</sup>

Unfortunately, sickle-cell disease and carrier screening programs "evolved in a rapid, haphazard, often poorly planned fashion, generated in large measure by public clamor and political pressure," as a National Academy of Sciences report in 1975 pointed out.<sup>35</sup> Several deficiencies in the screening programs contributed to their problems. First, the objectives of the programs were often not clear. Second, the target populations were often poorly chosen. For example, screening school-children, who would make little use of the information, was found to be counterproductive. Third, a lack of full protection of confidentiality in some programs led to stigmatization and misunderstandings. Most important, inadequate genetic counseling and public education resulted in misconceptions about the difference between being a sickle-cell carrier (who is typically not at any increased health risk) and having sickle-cell disease (which can be very debilitating and even fatal).

Unlike Tay-Sachs disease, prenatal diagnosis was not available for the hemoglobin disorders when carrier screening was first being developed.<sup>36</sup> Consequently the only way a couple identified as both being carriers could avoid the risk of having a child with sickle-cell anemia was to forego natural childbearing. As the screening programs were being promoted at a time of rising racial tension in the United States, the implication that certain blacks should not have children was seen by some members of the community as having hidden

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<sup>32</sup> G. Stamatoyannopoulos, *Problems of Screening and Counseling in the Hemoglobinopathies*, in A. Motulsky and W. Lenz, eds., *BIRTH DEFECTS: PROCEEDINGS OF THE 4TH INTERNATIONAL CONFERENCE (VIENNA, 1973)*, Medica, Amsterdam (1974).

<sup>33</sup> Ira M. Rutkow and Jeffrey M. Lipton, *Mandatory Screening for Sickle-Cell Anemia* (Letter), 289 *NEW ENG. J. MED.* 865 (1973).

<sup>34</sup> Pub. L. No. 92-294, 86 Stat. 136 (1972).

<sup>35</sup> GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH, *supra* note 13, at 117.

<sup>38</sup> Today, prenatal diagnosis for hemoglobinopathies is being developed. See pp. 24-28 *infra*. Particularly promising are techniques employing genetic engineering; these are described more fully in the Commission's report *SPLICING LIFE*, *supra* note 2.

racist motivations. Thus, for many people the overall impact of sickle-cell carrier screening was negative: rather than providing information that enhanced choices, screening seemed merely to burden the people screened.

This problem was accentuated because the early programs did not encourage community-based involvement, so neither the public nor physicians were well prepared to deal with the consequences of a “positive” finding from a screen. As during the first days of PKU testing in the early 1960s, the sudden public awareness of a simple test to aid in “preventing” disease led to pressure to test all susceptible individuals. The immense difference between being able to control PKU through diet and having to provide counseling on reproduction for sickle-cell carriers was not fully appreciated until later.

*Contrasting the Tay-Sachs and sickle-cell programs.* A variety of factors contributed to the relative success of Tay-Sachs carrier screening and to the contrasting failure of early carrier screening for sickle cell in the United States. Tay-Sachs disease varies little in its clinical course; progressive central nervous system degeneration culminates in death within a few years despite medical and nursing care; not even a palliative treatment is available for the disease. Sickle-cell anemia, on the other hand, varies in severity; progress is being made in developing treatments to avoid or ameliorate its symptoms and in extending the life span of affected individuals. Indeed, the variation is such that the disease may go unrecognized in some individuals with sickle-cell anemia. Consequently, in contrast to Tay-Sachs, avoiding the birth of a child with sickle-cell anemia was less widely regarded in the relevant population groups as obviously desirable.

Another significant failing of the first sickle-cell programs was the deficiency in public education and genetic counseling. Because a few carriers—classified as having the “sickle-cell trait” rather than sickle-cell disease—were reported to have experienced medical problems, being a carrier was regarded by many people as a personal health hazard even though the heterozygote very rarely, if ever, manifests any medically significant adverse effects. Misinformation about the sickle-cell trait precipitated psychological and social disabilities for known carriers. And when test results were not kept confidential, the problems of carriers were compounded. For example, job discrimination against carriers arose soon after screening programs were initiated, and questions were raised about their suitability for service in the armed forces.<sup>37</sup>

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<sup>37</sup> *Sickle Cell—Point, Counterpoint* (Editorial), 289 NEW ENG. J. MED. 323 (1973); *Grounded for Bearing Sickle Cell Trait*, WASH. POST, Dec. 26, 1980, at A-9.

In sum, early sickle-cell screening programs were ineffective and not readily accepted by the target population because they were often not community-based, did not build on adequate education, were mandated in some states in a hasty manner, and seemed to be aimed at preventing the birth of minority children.

**Prenatal Screening.** The era of prenatal diagnosis of genetic disorders and congenital defects was launched in 1966 with the report of the first chromosomal study of cultured cells withdrawn from an amniotic sac by amniocentesis.<sup>38</sup> In 1967 the first report of diagnosis of chromosomal disorders from cultured amniotic fluid cells appeared; the following year diagnosis of an inborn error of metabolism using amniotic fluid cells was reported.<sup>39</sup> Since then, prenatal diagnostic technologies have expanded at an astounding rate; more than 190 metabolic defects and congenital disorders can be diagnosed prenatally, in addition to an increasing number of chromosomal aberrations.<sup>40</sup> These developments, in turn, have speeded the evolution of a new area for medical intervention—prenatal therapy and surgery.

**Amniocentesis.** During amniocentesis, a small amount of amniotic fluid is withdrawn through a needle inserted through the uterine wall into the amniotic sac. The object is to obtain cells that have been generated by the fetus, although contamination of the fluid with maternal cells from outside the sac occasionally occurs. Serious maternal or fetal complications and the fetal mortality associated with the procedure at experienced centers are less than 0.5%.<sup>41</sup>

Prenatal diagnosis by amniocentesis is done for a variety of reasons, usually when an increased risk of a particular disorder—either chromosomal or an inborn error of metabolism—has been identified. To date, amniocentesis is most commonly done to assess fetal chromosomes. Cells extracted from the amniotic fluid are grown in a culture medium for several weeks and then studied for abnormalities that are suspected because of:

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<sup>38</sup> M. Steele and W. Breg, *Chromosome Analysis of Human Amniotic Fluid Cells*, 1 LANCET 383 (1966).

<sup>39</sup> Jacobson and Barter, *supra* note 8; H.L. Nadler, *Antenatal Detection of Hereditary Disorders*, 42 PEDIATRICS 912 (1968).

<sup>40</sup> S. Stephenson and D. Weaver, *Prenatal Diagnosis—A Compilation of Diagnosed Conditions*, 141 AM. J. OBSTET. GYNECOL. 319 (1981).

<sup>41</sup> National Institute of Child Health and Human Development, ANTENATAL DIAGNOSIS: REPORT OF A CONSENSUS DEVELOPMENT CONFERENCE, Dept. of Health, Education and Welfare, Washington (1979) at I-66. This figure is based on American and Canadian studies; a British study shows complication rates of 1-2%, but the design of that research has been widely criticized. *Id.*

- (1) “advanced maternal age”<sup>42</sup>;
- (2) a previous pregnancy that resulted in the birth of a chromosomally abnormal child;
- (3) a parent known to have or carry a chromosomal abnormality;
- (4) a family history of Down syndrome or other chromosomal abnormality;
- (5) a history of three or more miscarriages particularly if they occurred early in the pregnancies or were known to be associated with a chromosomal disorder; or
- (6) previous children (usually deceased) with multiple malformations on whom chromosomal analyses were not done.

When prenatal diagnosis is used to check for inborn errors of metabolism, the “high-risk” couples are those who have been identified by carrier screening, family history, or the prior birth of an affected child. As each test is specific for a particular disorder, it is imperative to know in advance which condition the fetus is at increased risk for, because an assay of the cultured cells for one condition will not reveal the presence of others.

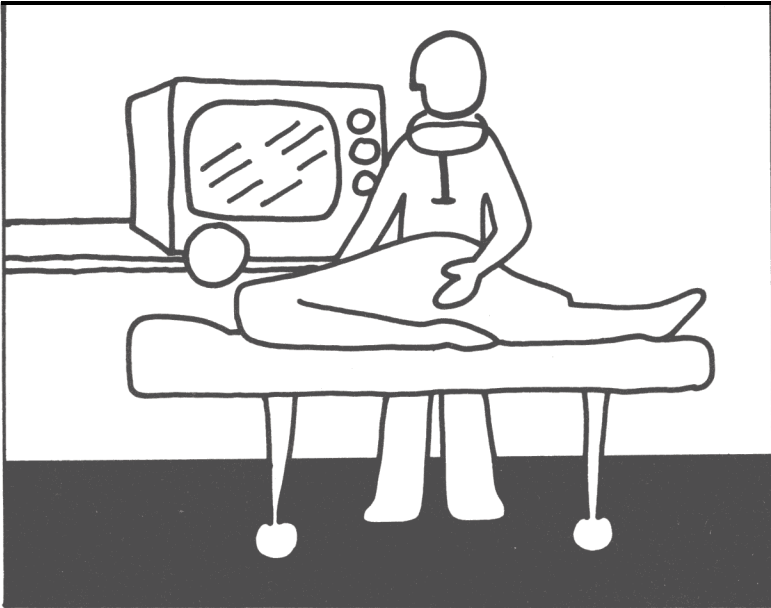
The laborious process of culturing amniotic fluid cells and examining their chromosomes or gene products requires specially trained technicians. The time-consuming and specialized nature of the tests has been an important limit on the availability of this type of prenatal testing. An experienced technician using automated equipment can process about 50,000 blood samples from newborns a year for PKU, but an experienced cytogenetics technician can complete about 150-200 prenatal chromosomal analyses annually.<sup>43</sup>

Until recently, amniocentesis was useful only for diagnosing genetic or chromosomal defects that showed up in cultured amniotic fluid cells. This limitation excluded disorders of specialized cells, such as the hemoglobinopathies, including sickle-cell anemia and thalassemia. Attempts were made—some successfully—to diagnose these disorders by withdraw-

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<sup>42</sup> “Advanced maternal age” is usually defined by physicians as being 35 years of age or older, but see pp. 75-81 *infra*. Maternal age is a concern because a woman’s risk of having a baby with a trisomy (particularly, Down syndrome) increases with her age. In recent years, increased attention has been paid to the contribution that males may make to the occurrence of chromosome aneuploidies in their children.

<sup>43</sup> John L. Hamerton and Nancy E. Simpson, eds., *Report of an International Workshop Held at Val David, Quebec, Nov. 4-9, 1979*, PRENATAL DIAGNOSIS: PAST, PRESENT AND FUTURE 16 (Special Issue, 1980); ANTENATAL DIAGNOSIS: REPORT OF A CONSENSUS DEVELOPMENT CONFERENCE, *supra* note 41, at I-59.



ing a small blood sample from the fetus, but this method is technically much more difficult and is far riskier than amniocentesis. In the last few years, however, researchers have developed new techniques for the prenatal diagnosis of sickle-cell anemia that make direct use of the DNA in amniotic fluid cells.<sup>44</sup> These methods, which are still experimental, reduce the risks associated with other testing methods and expand the availability of testing.

**Fetoscopy.** Direct visualization of the fetus and placenta *in utero*, a technique known as fetoscopy, was introduced as a transabdominal diagnostic procedure in 1973.<sup>45</sup> The procedure involves inserting into the amniotic sac a hollow needle that contains a device through which the fetus can be viewed. Even

<sup>44</sup> The sickle-cell gene was found often to be linked to a particular DNA sequence in the region of the gene responsible for hemoglobin production, which served as a surrogate "marker" for the sickle-cell gene when the DNA was broken down into measurable strands. Y.W. Kan and A.M. Dozy, *Antenatal Diagnosis of Sickle Cell Anemia by DNA Analysis of Amniotic Fluid Cells*, 2 LANCET 910 (1978). More recently, a method was developed that facilitates identification of the mutation directly, rather than by its association with a marker. This newer technique eliminates the need for the family studies that are required when markers are used in the diagnosis. Judy C. Chang and Y.W. Kan, *A Sensitive New Prenatal Test for Sickle-Cell Anemia*, 302 NEW ENG. J. MED. 30 (1982).

<sup>45</sup> J. Hobbins and M. Mahoney, *In utero Diagnosis of Hemoglobinopathies, Technic for Obtaining Fetal Blood*, 290 NEW ENG. J. MED. 1065 (1974).



in the most experienced hands, there remains a 3-5% miscarriage rate with the procedure.<sup>46</sup> An area of only two to four square centimeters can be seen through the fetoscope, which limits the ability to detect structural defects of the fetus. When a thin needle is inserted alongside the fetoscope, however, samples of fetal blood can be drawn from a vessel on the surface of the placenta. (Fetoscopy is not the only way fetal blood sampling can be accomplished; it can also be done using ultrasound to visualize the placenta.)

Prior to the introduction of DNA-related methods to detect hemoglobinopathies using amniotic fluid, fetoscopy provided the only prenatal diagnosis for these disorders. It has been used widely, particularly in Mediterranean countries, to detect thalassemia.<sup>47</sup> It is still important in disorders that are not diagnosable by other means, such as hemophilia.

Fetoscopy is also used to perform fetal skin biopsies. And it has played a part in some of the fetal surgery procedures recently performed on an experimental basis for conditions that must be treated prior to birth if irreversible damage is to be avoided.<sup>48</sup>

**Ultrasonography.** The first reports of the use of ultrasonography to explore structures of the human body appeared in the 1950s.<sup>49</sup> Today, prenatal genetic screening is one of the many fields of medicine in which visualization of internal structures is useful.<sup>50</sup> The viewing method is based upon the fact that pulses of ultrasound are reflected differently at the boundaries of media that differ in penetrability; the difference is determined by the density of each medium and the velocity of the ultrasound through it. The reflections of ultrasound waves from the boundary between bone and soft tissue, for example, would return with a greater intensity than those from the boundary between the kidney and other soft tissues. The variations in reflections, when combined electronically and projected on a television screen, create an image of the fetus or other area under study.

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<sup>46</sup> M. Mahoney, Presented at the Workshop on Prenatal Approaches to the Diagnosis of Fetal Hemoglobinopathies, Los Angeles, Calif., 1978.

<sup>47</sup> Y.W. Kan, M.S. Golbus, and A.M. Dozy, *Prenatal Diagnosis of beta Thalassemia: Clinical Application of Molecular Hybridization*, 295 NEW ENG. J. MED. 1165 (1976).

<sup>48</sup> Gary D. Hodgen, *Antenatal Diagnosis and Treatment of Fetal Skeletal Malformations*, 246 J.A.M.A. 1079 (1981).

<sup>49</sup> D. Howry *et al.*, *The Ultrasonic Visualization of Carcinoma of the Breast and Other Soft Tissue Structures*, 7 CANCER 345 (1954); J. Wild and J. Reid, *Echographic Visualization of Lesions of Living Intact Human Breast*, 14 CANCER RES. 277 (1954).

<sup>50</sup> For a brief but comprehensive review of ultrasonography and its uses in prenatal diagnosis, see ANTENATAL DIAGNOSIS: REPORT OF A CONSENSUS DEVELOPMENT CONFERENCE, *supra* note 41, at I-92-108.

In prenatal screening, a transducer is passed back and forth over the woman's abdomen, producing multiple views of the fetus on a small screen. The procedure causes no discomfort to the woman, and no adverse effects of ultrasound on the woman or fetus have been documented. Ultrasonography is used to examine a fetus, to establish the gestational age (by obtaining a head measurement), or to locate fetal structures before amniocentesis or fetoscopy is performed. As a type of prenatal genetic screening, ultrasonography has been used to examine fetuses at increased risk of such structural abnormalities as neural tube defects.

Increasingly, ultrasonograms are being used as a routine part of prenatal monitoring; this results in more diagnoses by early in the second trimester of pregnancy of minor conditions (such as cleft palate and other correctible defects) and of fetal sex.

**Alpha fetoprotein screening.** Neural tube defects (NTDs) are the result of incomplete closure of the neural tube (the fetal precursor to the spinal cord) and are among the most common birth defects in the United States. The two major forms of NTDs are anencephaly, in which the brain or skull are missing or incomplete, and meningocele (spina bifida), in which the spinal cord is exposed or improperly formed. Anencephaly and spina bifida each have an incidence in this country of about one per 1000 live births.

Anencephaly is a fatal condition; affected infants survive only hours or, at most, days. Spina bifida is associated with mental and physical defects ranging in degree from mild to severe. The condition often involves serious handicaps, such as mental retardation, lower limb paralysis, and lack of bowel and bladder control. Important strides have been made in alleviating some of these conditions with a series of surgical operations starting in infancy, as well as with intensive rehabilitative therapy.

NTDs are presumed to have a multifactorial etiology, although the precise cause is not known.<sup>51</sup> Unlike sickle-cell or Tay-Sachs disease, there is no well-defined high-risk population among Americans. (Individuals with a family history are at increased risk, but they account for only a small percentage of NTD births.)

Alpha fetoprotein (AFP) is believed to be involved in the fetal immunological system. In 1972 British researchers reported an abnormally high level of AFP in the amniotic fluid

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<sup>51</sup> Recent studies have sparked interest in the possible role of vitamin supplementation in the prevention of neural tube defects. R.W. Smithells *et al.*, *Apparent Prevention of Neural Tube Defects by Periconceptional Vitamin Supplementation*, 56 ARCH. DIS. CHILD. 911 (1981).

surrounding fetuses with NTDs; subsequently, correlations were also noted between elevated levels of AFP in maternal blood and fetuses with one of these conditions.<sup>52</sup> The increased levels of AFP in maternal blood are not found only in the case of NTDs, however; other complications of pregnancy, congenital defects, multiple births (since more than one fetus is contributing AFP), and fetal death are also associated with elevated levels.<sup>53</sup> Moreover, AFP levels in blood and amniotic fluid are different during, each week of pregnancy. The AFP level must be evaluated, therefore, in relation to a "normal" level for the particular gestational age; an inaccurate assessment of gestational age can lead to an incorrect interpretation of the AFP level. For these reasons, testing the level of AFP in a pregnant woman's blood—itself a fairly simple test—is only the first step in prenatal screening for NTDs, and is not diagnostic.

The next procedures in this screening are aimed at eliminating other possible explanations. First, a repeat blood test is done. If that is positive, it is followed by an ultrasound examination to confirm gestational age and determine whether multiple fetuses or fetal death is causing the positive test results. If these explanations of elevated AFP levels are eliminated, amniocentesis and a measurement of AFP in the amniotic fluid are appropriate. The expense, risks, and limited availability of amniocentesis restrict its usefulness as a screening tool for the general population. Although the amniotic fluid test is highly accurate, tests to confirm a positive result are being explored.<sup>54</sup> All these procedures must be completed between the 14th and 22nd weeks of pregnancy.

In the mid-1970s a large collaborative study of AFP screening in the United Kingdom (where the incidence of NTDs

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<sup>52</sup> D. Brock and R. Sutcliffe, *Alpha Fetoprotein in the Antenatal Diagnosis of Anencephaly and Spina Bifida*, 2 LANCET 197 (1972); A.E. Leek *et al.*, *Raised Alpha-fetoprotein Maternal Serum with Anencephalic Pregnancy*, 2 LANCET 385 (1973); D.J.H. Brock, A.E. Bolton, and J.M. Monaghan, *Prenatal Diagnosis of Anencephaly Through Maternal Serum-alpha-fetoprotein Measurement*, 2 LANCET 923 (1973).

<sup>53</sup> David J. Brock *et al.*, *Significance of Elevated Mid-trimester Maternal Plasma Alpha-Fetoprotein Values*, 1 LANCET 1281 (1979); B. Kjessler *et al.*, *Alpha-Fetoprotein (AFP) Levels in Maternal Serum in Relation to Pregnancy Outcome in 7,158 Pregnant Women Prospectively Investigated During Their 14th-20th Week Post Last Menstrual Period*, 69 ACTA OBSTET. GYNECOL. SCAND. 25 (1977); D.L. Hay *et al.*, *The Relation Between Maternal Serum Alpha-Fetoprotein and Feto-Maternal Hemorrhage*, 86 BRIT. J. OBSTET. 8 GYNECOL. 516 (1979). In some cases of spina bifida, a flap of skin covers the protruding spinal cord; AFP levels are not sensitive to these closed lesions.

<sup>54</sup> J.N. Macri, J.E. Haddow, and R.R. Weiss, *Screening for Neural Tube Defects in the United States: A Summary of the Scarborough Conference*, 133 AM. J. OBSTET. GYNECOL. 119 (1979).

is more than double the rate in the United States) yielded statistical information useful for implementing a program in the UK.<sup>55</sup> AFP screening is being offered by many local health authorities in that country, although some articles have appeared in recent publications questioning whether the test is beneficial in regions with a lower incidence of NTDs.<sup>56</sup> In 1979 a national task force recommended against rapid progress toward a countrywide program because of "uncertainties and costs entailed."<sup>57</sup> As part of the country's National Health Service, laboratories are centralized, the services involved in screening are coordinated, and the costs to those screened are covered. These differences in the health care system and in the scope of studies in the UK have led some researchers to argue that the British experience with AFP screening may differ significantly from what could be expected in this country.

In the United States, women who undergo amniocentesis for other indications typically also have the amniotic fluid tested for AFP; maternal blood testing is available only on a limited research basis. AFP test kits cannot be marketed because the Food and Drug Administration (FDA) has failed to approve them as safe and effective for general use. The reagents now in use are provided free by the manufacturer for research purposes or are prepared by the laboratory or obtained abroad. FDA's failure to provide premarket approval is in part a response to comments from a wide array of health professional groups, consumer organizations, and other agencies in the Public Health Service that maintain that unrestricted use of maternal AFP test reagents is premature and would lead to serious harm.<sup>58</sup> The general thrust of the objections has been that the potential demand for coordinated, high-quality services (including laboratories, extensive counseling, ultra-

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<sup>55</sup> Report of the UK Collaborative Study on Alpha-Fetoprotein in Relation to Neural Tube Defects, *Maternal Serum Alpha Fetoprotein Measurement in Antenatal Screening for Anencephaly and Spina Bifida in Early Pregnancy*, 1 LANCET 1323 (1977); Second Report of the UK Collaborative Study on Alpha Fetoprotein in Relation to Neural Tube Defects, *Amniotic Fluid Alpha-Fetoprotein Measurement in Antenatal Diagnosis of Anencephaly and Open Spina Bifida in Early Pregnancy*, 2 LANCET 651 (1979).

<sup>56</sup> Susan J. Standing *et al.*, *Maternal Alpha-Fetoprotein Screening: Two Years' Experience in a Low-Risk District*, 283 BRIT. MED. J. 705 (1981); Bryan Hubbard and C.J. Roberts, *Maternal Alpha Fetoprotein Screening* (Letter), 283 BRIT. MED. J. 1053 (1981).

<sup>57</sup> Working Group on Screening for Neural Tube Defects, *Report*, Dept. of Health and Social Security, London, mimeo. (1979).

<sup>58</sup> The groups opposing unrestricted release of the test kits include the American College of Obstetrics and Gynecology, American Academy of Pediatrics, American Society of Human Genetics, Spina Bifida Association of America, Health Research Group, Centers for Disease Control, Health Services Administration, and National Center for Health Care Technology. 45 Federal Register 74158 (Nov. 7, 1980).

sound, and amniocentesis) in a short time frame cannot be met. In other words, offering the test now would be premature since physicians and the public are not sufficiently familiar with the steps required and the significance of the test results.<sup>59</sup> Those objecting contend that these limitations would result in considerable parental anxiety, unnecessary abortions, and further inequities in health care.

Since no high-risk group has been identified (other than women with a family history of NTD), all pregnant women are potential candidates for screening. AFP maternal blood screening could be the first mass screening of pregnant women in this country; the demand for services and professional and public education would be considerable. Although there is widespread recognition that preparations must be made if AFP screening is to move beyond the limited research phase to become widely available in the health care system, considerable disagreement exists about the precise nature of these preparations and, perhaps more important, about who can best ensure that the necessary safeguards are in place.

Some argue that the health care system and professions can assimilate the new test safely and effectively. In this view, the concerns raised are outside FDA's jurisdiction for the most part and the agency's delays are doing harm by depriving women of the benefits of a valuable test. Others contend that responsibility for preventing harm from premature availability of the test properly lies with the FDA as part of its statutory requirement to establish the safety and effectiveness of certain medical devices before they are marketed.<sup>60</sup> The FDA has, however, neither approved nor rejected applications for AFP test kits that have been pending for several years. On

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<sup>59</sup> A recent study gave support to concerns about physician education and AFP testing. Testimony of Claire O. Leonard, transcript of 9th meeting of the President's Commission (May 8, 1981) at 78-79. A group of physicians in the Baltimore area were provided with written material about NTDs and AFP testing. In addition, oral presentations were made at a professional society meeting and at local hospitals. About half of the 108 physicians in the study attended at least one of these oral presentations. Despite these extensive efforts to educate physicians about a new test that they could perform, a follow-up questionnaire revealed significant gaps in the knowledge necessary for high-quality AFP testing. For example, only about half the physicians knew at what stage in a woman's pregnancy to draw the first blood sample; only about one-quarter knew the chance of an affected pregnancy after one positive blood test; only about one-third knew that the incorrect estimate of gestational age could cause a false positive; and just a few knew that ultrasonography was the recommended follow-up procedure.

<sup>60</sup> Federal Register, *supra* note 58; Council on Scientific Affairs, *Maternal Serum Alpha-Fetoprotein Monitoring*, 247 J.A.M.A. 1478 (1982).

November 7, 1980, FDA proposed for public comment a complex set of restrictions on use of the kits that was intended to address some of the concerns raised,<sup>61</sup> but as of January 1983 no final action had been taken on this proposal. Meanwhile, professional medical associations, such as the American College of Obstetrics and Gynecology, have started to educate their members about AFP testing.

The controversy over AFP testing points up many of the difficult, important, and as-yet-unresolved questions about implementing large-scale screening programs. These questions take on added importance in light of the likely development of other genetic screening tests involving large segments of the population.

In summary, the field of prenatal diagnosis has expanded considerably. Genetic service centers, supported in part under the National Genetic Diseases Act, performed amniotic fluid analyses on 42,003 specimens in 1979 and 1980.<sup>62</sup> Nevertheless, it is estimated that less than half the pregnant women for whom amniocentesis is considered medically appropriate are receiving it.<sup>63</sup> Furthermore, the expansion of available services to meet this demand is actually likely to broaden the category of "medically appropriate," just as demand will also increase through development of new diagnostic tests that permit services to be offered to patients with other genetic conditions.

#### **Emergence of Ethical Guidelines and Federal Legislation.**

The blossoming of medical genetics that began in the 1960s drew increased public and professional attention to the potential benefits of genetic screening and counseling. With this attention came recognition of the ethical implications of genetics programs. Some of these concerns were unique to genetic screening and counseling, while others were familiar issues, such as those raised generally by biomedical research with human subjects and by abortion.<sup>64</sup> The uncertainties discussed went beyond those of the ethics of individual

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<sup>61</sup> Federal Register, *supra* note 58.

<sup>62</sup> In 66% of these, advanced maternal age was the reason for the amniocentesis.

<sup>63</sup> S.J. Sepe *et al.*, *Genetic Services in the U.S. 1979-80*, 248 J.A.M.A. 1733 (1982).

<sup>64</sup> In this Report, the Commission addresses primarily issues particular to genetics programs. Research concerns are treated in the Commission's biennial reports on the protection of human subjects. PROTECTING HUMAN SUBJECTS, U.S. Government Printing Office, Washington (1981); IMPLEMENTING HUMAN RESEARCH REGULATIONS, U.S. Government Printing Office, Washington (1983). The debate about the ethics of abortion remains unresolved, but the issues have been explored at great length in many forums. It is not the purpose of this Report to rehearse those arguments or to try to resolve them but rather to examine genetic screening and counseling programs within the current legal framework.

patient-provider relations to encompass questions about the proper role of the state in protecting well-being and in respecting individual liberty.

Similar issues had been raised during the consideration of the PKU legislation in the mid-1960s but they received little attention then. The issues really came to center stage with the development and dissemination in the early 1970s of a simple screening test for sickle-cell trait, as the media forcefully spotlighted this “neglected disease.” Although many of the state and local screening efforts were initially supported by representatives of the black community, their enthusiasm waned as the manifest and potential problems with these efforts became clear.<sup>65</sup>

Federal officials had been promising to increase support for research on sickle-cell disease, so legislation pending in the Congress in 1972 became the focal point for responding to the perceived problems with existing programs. The resulting National Sickle Cell Anemia Control Act in May 1972 authorized funds for research and educational activities through fiscal year 1975.<sup>66</sup> Responding to complaints about the violation of individual rights by mandatory state screening programs, Congress limited Federal funding under this Act to those sickle-cell programs that were voluntary; not surprisingly, many states promptly changed their laws.

At the same time, a standing research group at the Institute of Society, Ethics and the Life Sciences (the Hastings Center) that had been studying ethical, social, and legal issues in genetic counseling recognized the need to develop guidelines for the operation of genetic screening programs. The impending expansion of genetic screening programs, and particularly the initiation of a national program, made this need even more urgent. Just nine days after the enactment of the Sickle Cell Act, the Hastings group published a report on “Ethical and Social Issues in Screening for Genetic Disease” in the *New England Journal of Medicine* that put forth the following rationale:

Since screening programs acquire genetic information from large numbers of normal and asymptomatic (e.g., carrier state) individuals and families, often after only brief medical contact, their operation generally falls outside the usual patient-initiated doctor-patient relation. As a result, traditional applications of ethical guidelines for confidentiality and individual physician responsibility are uncertain in mass screening programs. Thus, we believe it important that attempts be made now to clarify some ethical, social and legal questions

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<sup>65</sup> Stamatoyannopoulos, *supra* note 32.

<sup>66</sup> Pub. L. No. 92-294, 86 Stat. 136 (1972).

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concerning the establishment and operation of such programs.<sup>67</sup>

Like most analyses of this field, the report by the Hastings group combined ethical and practical considerations. It proposed guiding principles for the design and operation of screening programs drawn in part from the early experiences of PKU, sickle-cell, and Tay-Sachs programs. The article discussed the need for pilot projects, community participation, adequate testing procedures, and the protection of target populations. The importance of nondirective genetic counseling and education in screening programs was also emphasized.

The same year, at the request of the Social Issues Committee of the American Society of Human Genetics, the National Academy of Sciences asked its operating arm (the National Research Council) to establish a Committee for the Study of Inborn Errors of Metabolism to survey PKU screening and the effectiveness of dietary treatment. In addition, the Committee was asked to examine screening for other genetic diseases and to study the relationship between genetics and preventive medicine. The Committee first met in August 1972; in 1975, after more than a dozen meetings and workshops, it published a final report with detailed procedural guidance from both a practical and an ethical vantage point.<sup>68</sup>

Among other points, these investigations made it clear that there was no reason to separate sickle-cell anemia from other genetic disorders. In April 1976, the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Diseases Act was enacted,<sup>69</sup> which broadened the earlier statute on sickle-cell disease by authorizing activities on a wider range of genetic diseases through fiscal year 1978. The genetic diseases act was extended in 1978 to provide for basic and applied research, training, testing, counseling, and information and education programs for a wider range of genetic diseases.<sup>70</sup>

In fiscal years 1979 and 1980, 34 state genetic service programs received funds through the National Genetic Diseases Act. During those two years 131,818 at-risk individuals received genetic counseling. Screening programs for the detection of inborn errors of metabolism reported tests of 3,158,521 samples. Nationally, 195 children with PKU were detected, 536 with hypothyroidism, 25 with galactosemia, 8 with maple syrup urine disease, and 8 with homocystinuria. Prenatal diagnosis

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<sup>67</sup> M. Lappé *et al.*, *Ethical and Social Issues in Screening for Genetic Disease*, 286 *NEW ENG. J. MED.* 1129 (1972).

<sup>68</sup> GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH. *supra* note 13.

<sup>69</sup> Pub. L. No. 94-278, 90 Stat. 407 (1976).

<sup>70</sup> Pub. L. No. 95-626, 92 Stat. 3583 (1978).



by amniocentesis was performed on 42,003 samples, and 436 abnormal fetuses were detected.<sup>71</sup>

The National Genetic Diseases Act was superseded in 1981 by the Omnibus Budget Reconciliation Act<sup>72</sup>; Federal funds for genetic services, research, and professional training were included as part of the Maternal-Child Health (MCH) block grant. This change dramatically alters the Federal role in genetics. First, genetics programs must now compete with other maternal and child health services, with no guarantee of continuing support for the genetics component. Second, decisions about how to use most of the MCH money will be made at the state level; 85% of the MCH funds will go to the states. The remaining 15% covers the range of Federal activities relating to maternal and child health, including genetics.<sup>73</sup> As a result of these administrative changes, and of overall funding cutbacks, the Federal government in fiscal year 1982 provided limited funding to 25 state programs in their fourth year of funding to allow for an orderly phaseout of Federal support. There was no support for new programs.

These developments have raised concern in the medical genetics community over the resulting restrictions in services to patients. Many of these states have established well-organized, regionalized programs as recommended by the guidelines and the professional consensus of medical geneticists. Services have been coordinated in an attempt to minimize overlap and maximize efficiency. Funding that became available as a result of the National Genetic Diseases Act played an important role in the development of such programs, as intended, and concern is now being expressed that lack of funding will undermine the effectiveness of genetic screening.<sup>74</sup>

In 1979 the Hastings Center research group on genetics published another set of guidelines concerned specifically with the ethical, social, and legal issues in prenatal diagnosis.<sup>75</sup> The group examined a number of the issues raised by the rapid expansion in prenatal technologies and proposed guidelines "for the development and institutionalization of prenatal diagnostic programs and to help workers in this area provide

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<sup>71</sup> Sepe, *supra* note 63.

<sup>72</sup> Pub. L. No. 97-35, 95 Stat. 357 (1981).

<sup>73</sup> The 15% Federal set-aside is for special projects of regional and national significance (SPRANS), which includes genetic and sickle-cell service networks, hemophilia treatment centers, MCH training and research projects, pediatric pulmonary centers, and demonstration projects focusing on areas such as improved pregnancy outcome.

<sup>74</sup> Testimony of Dr. Kurt Hirschhorn, transcript of 18th meeting of the President's Commission (March 12, 1982) at 115-16.

<sup>75</sup> Tabitha M. Powledge and John Fletcher, *Guidelines for the Ethical, Social, and Legal Issues in Prenatal Diagnosis*, 300 NEW ENG. J. MED. 168 (1979).

the most favorable circumstances for thoughtful, informed, morally responsible decision making by parents.”<sup>76</sup>

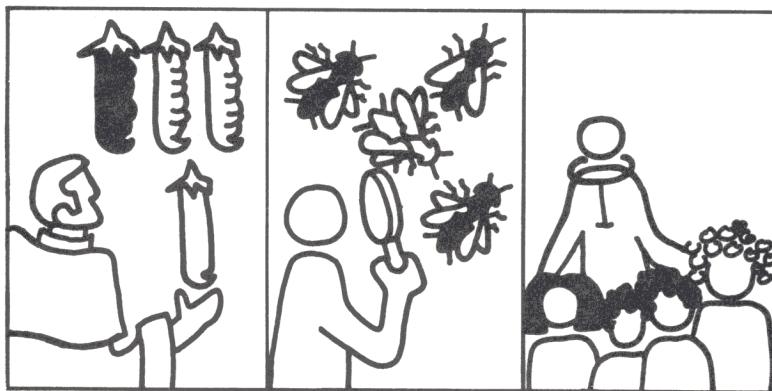
## Genetic Counseling Capabilities

**The Importance for Medicine of Counseling.** Although genetic counseling has a considerable history, it has taken on much greater significance in health care with the recent development of genetic screening techniques. As recently as 1963, one medical geneticist noted:

For the majority of therapeutically oriented physicians, genetic counseling holds no more attraction or significance than a number of other non-cure-directed activities that belong in the field of preventive medicine and are mainly designed to implement a public health program.<sup>77</sup>

Today, the value of genetic counseling as an integral part of genetic screening programs has been well established. And as more genetic tests are offered in the context of office visits, genetic counseling will take on greater importance for physicians.

Often patients' questions about reproductive risks or genetic disease in children arise first with a primary care physician (typically, an internist, family practitioner, or pediatrician) who must consider the need for a formal “genetic workup.” However, the primary care physician may lack the time, specific knowledge, and skills required for genetic counseling, so couples are frequently referred to a specially trained professional, often a member of a team at a medical genetics center.<sup>78</sup>



<sup>76</sup> *Id.* at 169.

<sup>77</sup> Franz J. Kallman, *Some Aspects of Genetic Counseling*, in Dept. of Health, Education and Welfare, *GENETICS AND THE EPIDEMIOLOGY OF CHRONIC DISEASE*, U.S. Government Printing Office, Washington (1965) at 385.

<sup>78</sup> F.C. Fraser, *Genetic Counseling*, 26 *AM. J. HUM. GENETICS* 636 (1974).

**The Emergence of Professional Counselors.** Until recently, a professional providing genetic counseling was typically a physician with an interest in genetics or a Ph.D. geneticist with an interest in medicine. In the past ten years, post-doctoral fellowship positions at major medical centers have prepared physicians and some Ph.D. geneticists in the full range of clinical genetics, including counseling. In addition, during the early 1970s a new category of genetic counselors with master's degrees (M.S.) emerged in response to a substantial increase in demand as screening and counseling programs grew and as the public and professionals became aware of the availability of such counselors. It was found that specially trained nonphysicians could successfully provide many of the genetic counseling services once supplied only by physicians. The special training for such counselors was formalized in 1969 with the establishment of the first master's degree program in genetic counseling at Sarah Lawrence College in Bronxville, New York.<sup>79</sup> Since then, several similar programs have been established at a number of other schools.

Either a well-trained nonphysician or a specially trained physician can be an effective genetic counselor; knowledge of human genetics, communication skills, and other, less easily measured personality-based factors are the characteristics needed. Usually, physicians who can diagnose genetic conditions and nonphysician genetic counselors work together on a team that includes the services of a variety of health professionals, including nurses, social workers, medical and research specialists, and laboratory technicians. Medical genetics teams have sometimes been expanded to include personnel at other hospitals or clinics associated with a central genetics facility. This extended team approach is useful for increasing public and professional access to genetic services.

The varied training and background of genetic counselors, and a recognition by the American Society of Human Genetics of the need for certification of counselors to maintain a suitable level of expertise in the field, led to the creation of a board certification process. Administered by the newly established American Board of Medical Genetics, separate tests are given for several categories of genetics professionals, including Ph.D. geneticists, medical geneticists, and genetic counselors. All providers of genetic services have been encouraged to take the examination. About 500 professionals passed the first

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<sup>79</sup> Bureau of Community Health Services, Public Health Service, *Genetics Associates—Their Training, Role and Function*, Dept. of Health, Education and Welfare, Washington, mimeo. (undated).

examination in December 1981; the test will be given next in June 1984.<sup>80</sup>

**The Counselor's Role.** The information-giving function is at the heart of genetic counseling, in most professionals' assessment, but the functional role of the genetic counselor has been vigorously debated. In addition to information-giver, several other paradigmatic "models"—such as moral advisor, or psychotherapist—have been offered.<sup>81</sup> These roles are not mutually exclusive, however, and the genetic counselor's role is generally viewed as a multifaceted one in which it will usually be desirable to incorporate elements of all the models.

The primary emphasis on information-giving is based on an ideal of "nondirectiveness," a goal that attempts to recognize the person counseled as an autonomous decisionmaker.<sup>82</sup> There are several possible explanations for this somewhat surprising norm of nondirectiveness among genetic counselors. First, directive genetic counseling became unpopular as a reaction to the "eugenic" misuse of genetic information during the early part of this century. Second, nonphysicians (who provided informal genetic counseling before it became a part of medical practice) apparently felt uncomfortable with the directive approach, even though many had stronger views than most doctors about the "right" outcome in terms of the impact of an individual's reproductive decisions on the genetic makeup of the population.

Finally, genetic counseling often involves topics of a highly personal nature, such as reproductive options and family planning; the value preferences inherent in such matters are more immediately apparent than is true in many other areas of medicine. This has apparently made genetic counselors more aware than practitioners who deal with less sensitive matters that making recommendations to clients could amount to an imposition of their own opinions or values and has underscored the importance of facilitating discussions based on the beliefs of the person being counseled.

Despite its history and rationale, nondirective counseling is challenged on a number of grounds. First, genetic counseling is being drawn more closely into the practice of medicine, and the emphasis on nondirectiveness contrasts with traditional

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<sup>80</sup> Information provided by personal communication with Dr. David Rimoin, President, American Board of Medical Genetics (1982).

<sup>81</sup> Y. Edward Hsia, *The Genetic Counselor as Information Giver*, in A.M. Capron *et al.*, eds., *GENETIC COUNSELING: FACTS, VALUES AND NORMS*, Alan R. Liss, Inc., for the National Foundation-March of Dimes, New York (1979) at 169; Seymour Kessler, *The Genetic Counselor as a Psychotherapist*, *id.* at 187; Sumner B. Twiss, *The Genetic Counselor as Moral Advisor*, *id.* at 201.

<sup>82</sup> Y. Edward Hsia *et al.*, eds., *COUNSELING IN GENETICS*, Alan R. Liss, Inc., New York (1979) at 283-84.

medical practice, in which physicians are more likely to suggest which course of action they consider preferable. Second, some people who receive genetic counseling exert pressure toward directiveness. In other contexts—such as job counseling or marriage guidance—the term “counseling” is used for consultations with professional advisors who are expected to provide not only psychological support but firm directions about problem-solving. Consequently, the expectations of some people who seek genetic counseling are not met.<sup>83</sup>

Moreover, it is probably impossible to achieve nondirectiveness; nonverbal and verbal suggestion of the course the counselor thinks is correct occurs both intentionally and unintentionally. And even genetic counselors who maintain that nondirective counseling is appropriate in most situations hold out certain exceptions. For example, when an otherwise competent person has become very upset by the information presented or shows a mistaken understanding or interpretation of it, some counselors believe the person should be told what to do.<sup>84</sup> Of course, such a judgment is a delicate matter, very dependent on the ability to distinguish a real breakdown in reasoning ability from a temporarily clouded judgment; furthermore, counselors must guard against treating as “irrational” any decision with which they disagree.<sup>85</sup>

Even with fully competent patients, some geneticists have argued that directive counseling against childbearing is sometimes appropriate. One frequently cited example is Huntington’s disease, an autosomal dominant disorder in which the symptoms (progressive, fatal neurological deterioration) ordinarily do not become apparent until during or after the childbearing years.<sup>86</sup> Consequently, people carrying the gene for it may pass the disorder on to their children before they are aware they have it themselves. When relatives of those with the disease seek genetic counseling to learn their risks, some

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<sup>83</sup> James R. Sorenson, Judith P. Swazey, and Norman A. Scotch, *REPRODUCTIVE PASTS, REPRODUCTIVE FUTURES: GENETIC COUNSELING AND ITS EFFECTIVENESS*, Alan R. Liss, Inc., for the March of Dimes Birth Defects Foundation, New York (1981).

<sup>84</sup> Robert R. Lebel, *Ethical Issues Arising in the Genetic Counseling Relationship*, 14 *BIRTH DEFECTS: ORIGINAL ARTICLE SERIES* (No. 9, 1978) at 29.

<sup>85</sup> For a further discussion of patient incapacity to make decisions, see Chapters Eight and Nine of the Commission’s Report, *MAKING HEALTH CARE DECISIONS*, U.S. Government Printing Office, Washington (1982).

<sup>86</sup> A patient with Huntington’s disease undergoes a series of mental, neurological, and motor changes that progressively worsen over 10-15 years and that culminate in death.

people argue that they should be strongly advised not to have children.<sup>87</sup> Since inheritance from a parent, rather than new mutations, accounts for more than 95% of the cases of Huntington's disease, the simplest and most effective way to reduce its frequency would be for anyone at risk for the disease (or known to have it) not to reproduce. However, placing primary emphasis on the benefits to society rather than to individual families connotes eugenics and contrasts with the goals of genetic counseling as they are generally understood today.

Plainly, genetic counseling is an expanding and evolving field. Based upon recent findings about the counseling process, changes can be expected to continue in the role of genetic counselors, as medical genetics assumes an increasing role in health care.<sup>88</sup>

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<sup>87</sup> *Genetic Counseling and the Prevention of Huntington's Chorea* (Editorial), 1 LANCET 147 (1982); T.L. Perry, *Some Ethical Problems in Huntington's Chorea*, 125 CAN. MED. ASSOC. J. 1098 (1981).

<sup>88</sup> See, e.g., Sorenson, Swazey, and Scotch, *supra* note 83; Idida Abramovsky *et al.*, *Analysis of a Follow-up Study of Genetic Counseling*, 17 CLINICAL GENETICS 1 (1980); G. Evers-Kiebooms and H. van den Bergil, *Impact of Genetic Counseling: A Review of Published Follow-up Studies*, 15 CLINICAL GENETICS 465 (1979).

The prevention and treatment of genetic disease has become an increasingly important component of health care. A growing number of genetic diseases can be accurately diagnosed, and more genetic information of potential value to individuals and families is now available. By providing this important information, well-designed and carefully implemented genetic screening and counseling programs give individuals greater opportunities to make informed, autonomous decisions about their own health and about reproduction. Screening and counseling programs can also make major contributions to public health and personal well-being by reducing the incidence of genetic disease and by facilitating more-effective management and treatment.

**Successful programs require concrete goals and specific procedural guidelines that are founded on sound ethical and public policy principles.** In this chapter, the Commission articulates these principles and uses them to clarify some of the more important ethical and legal issues presented by the ever-increasing role of genetic screening and counseling in medical care and public programs. The main ethical principles are autonomy, beneficence (including the prevention of harm), justice (including equity and fairness), and privacy (including confidentiality). The chief public policy principles are efficiency (or economy) and public participation (through democratic political institutions). These principles are neither controversial nor peculiar to genetic screening and counseling. Disagreement arises only when there is a conflict among some of them, and their content and relative weight must be specified more precisely.

Because the ethical, social, and legal issues raised by genetic screening and counseling are so diverse and are at various stages of development as matters of public policy, the

Commission's conclusions about them take different forms. On some points, the Commission has reached general conclusions that may be of interest to all concerned citizens and not just to patients, health care providers, or public officials. On other points, the Commission recommends that guidelines be adopted for genetic screening and counseling programs or that other steps be taken by legislative bodies. In each case, the Commission attempts to address its conclusions to particular groups among the wide range of players—from Federal officials to community organizers, from professional medical societies to primary school teachers. Some recommendations will best be carried out by professional medical organizations, such as medical specialty groups or medical school curriculum committees. Others are within the purview of state or Federal officials who have authority to allocate funds for screening and counseling programs. Still others apply to nonprofit organizations concerned with education, treatment, and research for genetic diseases.

### **Confidentiality**

There are three main areas of concern over confidentiality in genetic screening and counseling: (1) disclosure of information to unrelated third parties, such as employers or insurers; (2) access to material stored in data banks; and (3) disclosure of information to relatives of the screenee, either to advise them that they or their offspring are at risk for genetic disease or to gain information about them for a more accurate diagnosis of the person originally screened.

Questions about disclosure of genetic information to third parties sound familiar notes in the debates over medical confidentiality. **Because of the potential for misuse as well as unintended social or economic injury, information from genetic testing should be given to people such as insurers or employers only with the explicit consent of the person screened.**<sup>1</sup> Further, the agencies in question should develop forms for specific rather than blanket consent, to prevent unnecessary disclosures and to ensure the screenee selective control over access. The screenee should be told which information has been disclosed, to whom, and for what purpose.

The confidentiality of material stored in data banks is also not peculiar to genetics. Concerns about privacy are particularly acute regarding genetics, however, both because the poten-

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<sup>1</sup> When screening (genetic or nongenetic) is undertaken in the industrial setting at company expense in order to monitor workplace safety or employee suitability, access to the resulting medical record—by third parties, and even by the person screened—raises special issues that are currently being studied by other groups, such as the Congressional Office of Technology Assessment.



tial information involves particularly sensitive matters (such as personal identity and reproductive “fitness”) and because, in the case of “banks” of actual cell samples, it may be impossible at the time the material is placed in the system to know all the information that new tests might someday reveal. **Private and government agencies that use data banks for genetics-related information should require that stored information be coded**, whenever coding is compatible with the reasons the information is stored, both to preserve anonymity and to minimize the risk of unauthorized computer access.

The Commission focuses its attention in this Report on the release of information to relatives of the screenee, which in some cases raises issues of special significance in the context of medical genetics.

**Involuntary Disclosure to Relatives.** The issue of disclosing the results of genetic screening to relatives is raised when serious harm could be prevented by providing the relatives with information they would not otherwise be likely to obtain in a timely fashion. One example of this situation is the clinical diagnosis of multiple polyposis of the colon, a condition that is a precursor to cancer. Early detection and treatment—before the onset of symptoms—greatly improves the prognosis. Once the condition is detected clinically in one family member, therefore, the question is whether the physician, guided by the knowledge that the disease is genetic, should try to advise others in the family to be screened.

The issues raised by a patient’s refusal to allow test results to be used as a basis for contacting relatives depend on the circumstances. The narrowest claim for involuntary disclosure to relatives at increased risk would apply when it is known in advance that a test’s results could be uniquely helpful in preventing serious physical harm to relatives of the person tested. In such circumstances prospective screenees should be advised prior to testing of the value of informing at-risk relatives and efforts should be made to elicit their voluntary consent to disclosure. Making access to the test conditional upon prior agreement to disclose information may be justifiable. Conditional access would be easiest to justify in programs funded by private organizations. Since such groups are under no obligation to provide the service in the first place, it seems reasonable that they should be able to require a disclosure agreement as a condition of participation. In the case of publicly funded programs, the same policy might be justified on the grounds that even if citizens have a right to participate in the testing program, the right is not absolute and is limited by the state’s interest in protecting others from harm. Such a policy, however, might deter some people from participating. Consequently, a decision to require consent to disclosure must take into account the harm that might be done or the

benefits that might be foregone if some individuals chose not to participate.

A more difficult case arises when such an advance agreement has not been reached, as when genetic testing produces unexpected information that could benefit a person's relatives. People may oppose disclosure of results of their tests because they fear that the positive findings—or even their participation in the screening—could lead to stigmatization by relatives. In some cases, people may choose to withhold information because they believe their relatives would not want it. And some people are estranged from their families and do not want to do anything that might help their relatives or bring them back into contact with each another.

It might seem that a genetic counselor ought never to disclose information against the wishes of a client, because the counselor's professional obligation is to the client, not to others. Both the law and morality recognize, however, that a professional's primary obligation is in some circumstances subsumed by the need to prevent harm to others. Perhaps the clearest medical application of this principle is that of health providers' obligation to report communicable diseases. Genetic disease is not strictly analogous to communicable diseases, although it might be argued that the major difference is that transmission is "horizontal" in the one case and "vertical" in the other. Yet the relevant similarity is that in both cases the duty to prevent harm to others may in some instances place limits on the professional's duty of confidentiality.<sup>2</sup>

**A professional's ethical duty of confidentiality to an immediate patient or client can be overridden only if several conditions are satisfied: (1) reasonable efforts to elicit voluntary consent to disclosure have failed; (2) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (3) the harm that identifiable individuals would suffer would be serious; and (4) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.**<sup>3</sup> The individual's family history (pedigree) should be carefully analyzed to identify accurately any relatives at increased risk so that information is presented only to the appropriate individuals, and anonymity should be preserved wherever possible. Since the decision to breach professional

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<sup>2</sup> See, e.g., Almeta E. Cooper, *Duty to Warn Third Parties*, 248 J.A.M.A. 431 (1982).

<sup>3</sup> It is worth emphasizing that the harm-prevention argument for compelled disclosure merely shows that the commitment to confidentiality is not absolute in cases of the sort described. It does not establish that a general practice of breaching the confidentiality of genetic information would have acceptable consequences.

confidentiality is such a weighty one, it may also be advisable to seek review by an appropriate third party.

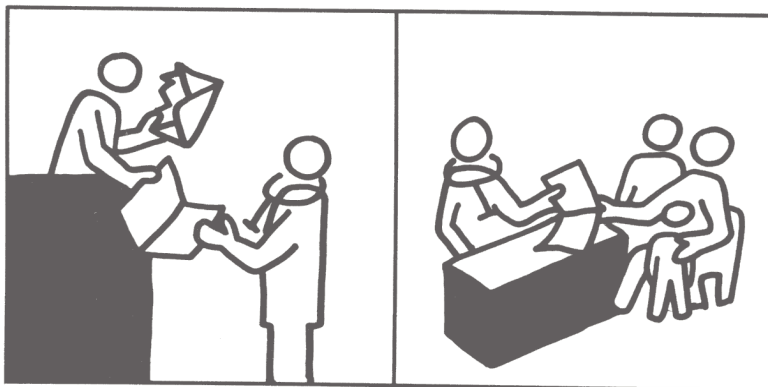
With improved public education about genetics, however, and appropriate genetic counseling in individual cases, it is hoped that involuntary disclosure will be infrequent. When a person understands that there is nothing shameful about a genetic disease or trait and that the information may be invaluable to relatives, either for their own health care or for their decisions about childbearing, willingness (or even eagerness) to share the information with relatives should increase.

Medical history is replete with examples of conditions once considered shameful or private and now openly discussed. The increased public awareness and education that led patients and physicians to say the word "tuberculosis" rather than refer vaguely to "a spot on the lung" and that has made the discussion of cancer more open could also reduce the stigma associated with genetic diseases.

**Release of Information in Case of Adoption.** Disclosure of information to relatives is more complicated when a sealed adoption record must be opened to locate the individual(s) at risk for a genetic condition. This may arise when a genetic condition identified in an adoptee bears on the health of members of the biological family or, the reverse, when a condition diagnosed in the biological family has implications for the health of the adoptee.

The laws governing adoption in all 50 states, the District of Columbia, Puerto Rico, and the Virgin Islands require adoption records to be sealed following adoption decrees as a way of protecting the confidentiality of both the biological and adoptive families. A family medical history typically is part of the required record, although specific reference to genetic information is generally not made. Moreover, sometimes a genetic condition does not become apparent until after the adoptive process is complete. For example, Huntington's disease, myotonic dystrophy, and other serious conditions may be diagnosed after the adoption proceeding; genetic counselors would then be concerned about the 50% risk that any child the person had given up for adoption has of developing such a disease. Such information can be conveyed to the relative at risk only if the adoptive record is unsealed.

Some adoption agencies or county courts that maintain adoption records may conclude that new genetic information renders the existing medical record incomplete and, therefore,



that the record should be unsealed and the information communicated to the adoptive family.<sup>4</sup> But most adoption laws were not written with such contingencies in mind; existing provisions may be inadequate to address the circumstances or to provide procedures under which the record can be unsealed so that genetic information can be communicated to either the biological or adoptive family. The US. Department of Health and Human Services' recent model state statute for "children with special needs" (that is, children with characteristics that constitute a barrier to adoption of the child) would require inclusion of a genetic history and provides for supplementing this material for at least 60 years after the child reaches the age of majority.<sup>5</sup> Provisions like these are needed for all adoptions. **The Commission recommends that law reform bodies, working closely with genetic professionals and organizations interested in adoption policies, seek changes in the adoption laws to ensure that information about serious genetic risks can be conveyed to adoptees or their biological families.**

**The Commission further finds that the goals of preserving confidentiality and preventing harm can best be advanced if genetic counselors act as mediators in the process of identifying relatives at risk and communicating relevant information.** The counselor already is part of a confidential relationship in which sensitive information about the risks of genetic disease are discussed. That "circle of secrecy" need only be extended slightly to the confidentiality that surrounds an adoption record if important genetic information is provided to the relatives by the counselor.<sup>6</sup> In most cases, the biological and

<sup>4</sup> Gilbert S. Omenn, Judith G. Hall, and Kenneth D. Hansen, *Genetic Counseling for Adoptees at Risk for Specific Inherited Disorders*, 5 *AM. J. MED. GENETICS* 157, 158-59 (1980).

<sup>5</sup> § 303(f)(5), Model Act for Adoption of Children with Special Needs; Final Legislation, 46 *Federal Register* 50022 (Oct. 8, 1981).

<sup>6</sup> A.M. Capron, *Tort Liability in Genetic Counseling*, 79 *COLUM. L. REV.* 619, 680 (1979).

adoptive families would not need to communicate personally or be identified. When such safeguards are in place, it seems likely that screenees would be willing to have genetic information released to relatives at risk on either side of an adoption.

## Autonomy

The Commission believes that the principle of autonomy, which holds a high place in Western ethical and legal traditions, is important not only in the relationships of individual patients and health care professionals (through the requirement of informed consent) but also in the choices that people make about the use of genetic services. Ethical and legal implications would therefore arise immediately were participation made compulsory by law, but they can also arise as a result of more subtle forms of pressure.

**Voluntary Programs.** One of the central ethical issues in screening and counseling is that of voluntariness. There are two main questions: Should participation in screening and counseling programs always be voluntary? Should treatment of genetic disease detected through screening always be voluntary? If the general legal and ethical requirement of informed consent for medical procedures is applied here, the answer to both questions would seem to be yes. Although four major arguments have been offered to justify compulsion, the Commission finds that only one—the protection of those unable to protect themselves—has any merit, and then only under special circumstances.

**To save society money.** Some might argue that compulsion is warranted if it is necessary for the control of health care costs. That is, individuals may rightly be compelled to participate in genetic screening and counseling and to undergo prenatal therapy or even abortion in order to minimize society's burden in caring for individuals with serious genetic defects. The chief objection to this argument is that it rests upon a general principle that few, if any, would wish to see consistently implemented—namely, that a person's freedom to make the most intimate choices, and even a person's very existence, depends upon the degree to which social utility is maximized. Even were it morally permissible to employ utilitarian calculations in the extreme circumstances of so-called lifeboat or triage situations, it would not follow that it is permissible to do so in a society as affluent as the United States, especially when other means of husbanding resources are available that do not pose such a direct and profound threat to the commitment to equal respect for individuals. **The Commission finds no basis in the maximization of social utility that justifies compulsory participation in genetics programs.** Rather than finding utilitarianism particularly appropriate in determining social policy on genetics programs, the contrary

appears to be the case, in light of the especially strong reasons to preserve individual liberty on matters of medical treatment and reproduction.

*To allocate resources fairly.* Alternatively, an attempt might be made to rest compulsory screening and treatment on an appeal to fairness rather than to social utility. Specifically, some may argue that it is unfair for an individual to exercise his or her freedom of choice so as to impose upon others the burden of caring for someone whose condition was avoidable. Those who fail to prevent genetic disease might be said to take unfair advantage of the contributions that others make to minimizing human suffering.

Though this argument avoids assuming that utilitarianism is the appropriate moral theory, it is unpersuasive for other reasons, particularly because it assumes that an individual who fails to undergo screening or treatment thereby *imposes* a burden on others. Two cases must be distinguished: those in which an adult will not voluntarily undergo screening to detect a genetic condition that, if undetected, may result in a deterioration of his or her own health, and those in which a genetic condition will adversely affect the health of an individual's children.

At present there may be few instances of the first sort of case, in which early detection through screening of an adult would allow preventive intervention or less-costly management of a late-onset disease, though future research may make this increasingly possible. An individual who refuses to be screened could argue that the refusal does not impose a burden on other people because it is up to them to decide whether or not to provide the additional care needed due to the disease not being detected at an earlier stage. Others may assume the burden if they wish, but if they do assume it then the individual cannot be said to impose it on them.

Similarly, since society may choose whether or not to allocate resources for the care of those with unhealthy lifestyles, it is wrong to say that those individuals impose a burden on society. Society can either assume the responsibility of treating the heavy smoker's lung cancer or refrain from doing so and allow the burden to fall upon the smoker. If a person knowingly acts in a way that incurs avoidable medical expenses for his or her own care, and would not have done so had he or she not been counting on society to pay the bill, the person is taking unfair advantage of the generosity of others. However, if a person waives any right to social support and is willing to bear the consequences of the behavior, then it cannot be said that the person is taking unfair advantage of society's generosity or that society has a right to prevent that behavior, so long as others are not directly harmed by it.

Nonetheless, even if the very great practical problems could be overcome of establishing a system in which individuals could waive their rights to public support for health care in order to avoid having to undergo procedures they object to, the public might find it difficult if not impossible to turn a cold shoulder once the consequences are manifest. Although it may be true that a society can choose whether to assume the burden of an individual's illness, or that an individual can relieve society of that burden, it does not necessarily follow that the society will have either the will to follow through on the implications of such a decision or the ability to do so in a manner that seems fair. Society has been notably unwilling to deny care (or even to place conditions on it) for cigarette-smoking patients who develop lung cancer. Nor, to cite another example, have any head injuries of motorcyclists who failed to wear helmets been left unattended.

In the second type of case—a genetic risk that manifests itself only in offspring—the “fairness” argument for compulsory screening and treatment is totally unconvincing because a parent cannot waive a child's rights. Although it may be irresponsible and unfair for an individual to create an *avoidable* drain on resources that could be used to relieve other instances of suffering, it would be even more unfair to punish children because of their parents' choices.

Again, it is important to distinguish two morally distinct cases of parental choice: those in which the costs to society of caring for a child with a genetic disease are reduced or avoided entirely through carrier testing and a decision not to conceive, and those in which the social costs in question are to be avoided by abortion following a positive prenatal test. For people with firm convictions against abortion, the latter course of action is never a morally permissible way to avoid social costs. Moreover, most people who do not oppose abortion when chosen by a pregnant woman herself would still reject a policy that might require other people to act contrary to their fundamental moral convictions for the sake of achieving a fairer distribution of social costs.

The “fairness” argument in the case of carrier testing is not so easy to dismiss, however, because foregoing conception would not require a woman to terminate a pregnancy. In fact, if artificial insemination or adoption are available and acceptable to the individual, the experience of parenting need not even be forfeited. Some couples, however, may place great value on the opportunity to bear and raise children that are biologically their own, even at the risk of genetic disease. In such cases, it is not at all clear that considerations of fairness in the distribution of social burdens would justify overriding this deep personal preference.

Even in other, less controversial areas, society has generally not restricted individual liberty on the grounds that certain behavior would result in avoidable social costs, unless the behavior is directly dangerous to others. Though personal responsibility for health is increasingly advocated, no serious attempt has been made to implement policies that would place the costs of smoking, alcohol use, or other dangers to health on the individuals who expose themselves to such risks or that would prohibit people from running these risks. Moreover, while experts disagree about whether smoking and alcohol consumption are voluntary enough to say that they represent free choices about behavior, being at risk for genetic disease is clearly not voluntary. Consequently, the case for compulsory screening and treatment of genetic diseases seems even more dubious than for restrictions on other risks.

Finally, there is a strong American tradition to give the benefit of doubt to the value of individual liberty, especially in matters of reproductive choice. For this reason, compulsory genetic screening and treatment seems the least likely place to begin a policy of coercion in the name of a fair distribution of the costs of health care. Although the "fairness" argument raises issues that deserve consideration in defining the scope of individual choice, it does not provide adequate grounds for mandatory genetic screening and treatment.

***To protect the helpless from harm.*** The most plausible case for compulsory participation in genetic screening and further interventions as necessary rests on the premise that society has an obligation to minimize serious and unambiguous harm to identifiable individuals who are unable to protect themselves.<sup>7</sup> Most states mandate screening for PKU and, in some cases, for other diseases as well.<sup>8</sup> But these tests only involve the taking of a small blood sample and are performed on the infants themselves, with the aim of preventing harm to them. The justification here is the same as for compulsory education, the assumption being that the state may act so as to protect the basic interests of minors; as in the case of education, the law in most states also explicitly recognizes

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<sup>7</sup> Compare Ruth R. Faden, Neil A. Holtzman, and A. Judith Chwalow, *Parental Rights, Child Welfare, and Public Health: The Case of PKU Screening*, 72 AM. J. PUB. HEALTH 1396 (1982) (argues on moral grounds against parental consent for newborn screening), with George Annas, *Mandatory PKU Screening: The Other Side of the Looking Glass*, 72 AM. J. PUB. HEALTH 1401 (1982) (focuses on improving parental understanding, not on coercion).

<sup>8</sup> National Clearinghouse for Human Genetic Diseases, STATE LAWS AND REGULATIONS ON GENETIC DISORDERS, Dept. of Health and Human Services, Washington (1980). As of 1980, PKU screening was mandatory in 48 states: two states and the District of Columbia have voluntary programs. For a discussion of conditions for which newborns are sometimes screened, see pp. 12-17 *supra*.



valid grounds (such as religious objections) on which parents may resist such tests. **Although a strong presumption prevails in favor of voluntary screening programs, the Commission concludes that programs requiring the performance of low-risk, minimally intrusive procedures may be justified if voluntary testing would fail to prevent an avoidable, serious injury to people—such as children—who are unable to protect themselves.**

When screening involves only the child's body (for example, newborn screening), it is not ethically acceptable to fail to prevent or relieve serious, irreversible harm to a child merely because parents refuse to allow the screening. A legislature following this principle could mandate newborn screening for genetic conditions if some proportion of parents consistently withheld their consent, even though they have been given appropriate information about the purpose, benefits, and extremely small risks of a test that yields information of great importance to the well-being of children. Determining the number of refusals that ought to trigger imposition of mandatory screening is a delicate public policy issue that turns on an ethical evaluation of facts and assumptions. A study of the effects of a voluntary program for PKU screening, instituted in Maryland in 1976, found that the rate of parental refusal was only .05%; the chance of missing a case because of parental refusal is 100 times less than missing one from false negatives that occur because of problems with the time of testing and so forth.<sup>9</sup>

An ethically more difficult case is raised when the contemplated intervention is prenatal or preconceptual and thus would involve the body of one or both prospective parents. On a personal level it would, of course, be appropriate to give prospective parents moral counsel and as much practical assistance as possible in order to prevent or ameliorate any avoidable harm to their children. But the justification of protecting defenseless third parties would have to be very weighty before parents' bodily integrity could be invaded over their objections. As the degree of bodily invasion increases (ranging from a premarital blood test that could alert a person to the need for voluntary steps to correct a reversible condition, for example, to amniocentesis in order to diagnose an untreatable condition), the severity of the predicted harm and the certainty that the intervention will prevent it must

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<sup>9</sup> Ruth R. Faden *et al.*, *A Survey to Evaluate Parental Consent as Public Policy for Neonatal Screening*, 72 AM. J. PUB. HEALTH 1347 (1982) (finds that shift to voluntary PKU screening, with parental consent, under Maryland statute did not make screening less persuasive or cost-effective; most mothers wanted to be informed of test in advance, although about half did not believe parental consent should be required).

likewise increase for an unconsented intervention to be ethically acceptable. As a legal matter, the constitutional right of privacy may erect an even more formidable barrier to forced testing.

The Commission has not found that any government programs of involuntary genetic screening and counseling of adults are presently being undertaken. Were such programs to be proposed as a means of protecting children, the first response should be to try to achieve the desired results through improvements in education and information for the public and health professionals and in the services available in voluntary genetics programs. Public efforts would be better directed at reducing infant morbidity associated with inadequate maternal nutrition or prenatal health care than at requiring genetic interventions simply because they are technologically available.

Similarly, even in the testing of children themselves for “protective” reasons, good results may depend more on the adequacy of support for planning and execution of the program than they do on its mandatory nature. In PKU testing and other screening that depends on subsequent tests to eliminate initial false positives, adequate follow-up is essential to meet screening goals. Deciding whether screening should be voluntary or mandatory should reflect, therefore, the expected ability not only to reach the target population for the initial test but also to provide needed follow-up services.

*To improve society's "genetic health."* Some people might contend that individuals may be compelled to participate in screening programs not only for the sake of preventing unambiguous, serious harms to particular individuals, but also in order to achieve a societal standard of “genetic health” or “genetic normality.” The weaknesses of this line of argument are manifold. Perhaps most importantly, the very notions of “genetic health” and “genetic normality” are extremely vague and elastic slogans that disguise controversial ideals of human excellence as value-free medical categories. Recent history illustrates how these notions, in the hands of repressive and exploitative political movements, can be used to justify extreme eugenic measures. Sound public policy—especially when it involves the curtailment of individual liberties—cannot be based on such loose and abusable notions. **The Commission concludes that mandatory screening cannot be justified on grounds of achieving a “genetically healthy society” or other similarly vague and politically abusable social ideals.**

**Subtle Societal Pressures.** Direct compulsion (through the imposition of economic burdens or through laws) is not the only way in which people may find their freedom restricted regarding genetics programs. Indeed, the attitudes and policies of health professionals and widely held social expectations

may be more significant factors in determining the choices people are able—or feel themselves able—to make. Reciprocally, the choices made by many independent individuals form new societal norms that are not the conscious creation of any one person. These in turn may not only impose significant limitations on people's choices in the future but may also alter basic societal attitudes and presumptions.

The ethical problems presented by this interplay of individual choices and social norms may be as unanticipated as the emergence of new social norms is unintended. In addressing this subject, the Commission does not believe it would be either wise or feasible to attempt to freeze social norms and individual options just as they are today. But an awareness of the manifestations of this synergistic relationship that it finds undesirable can help society take appropriate corrective steps, especially to preserve the voluntariness of genetics programs.

*Tensions between autonomy and collective goals.* Human genetics has passed through a period when the most personal reproductive choices were manipulated for social and political ends.<sup>10</sup> Genetic screening came of age when those memories were very fresh and that early history affects programs even now. Nondirective counseling is widely extolled and, except in isolated instances where a child could suffer severe injury or death, it is generally recognized that choosing whether to participate in screening and how to use the results should be fully voluntary.

Thus in principle genetic screening and counseling closely resemble other medical interventions that individuals choose to use to a greater or lesser extent, depending on the relevance of the information to their personal decisionmaking. As already discussed, there is also a decided public health aspect to genetic disease, however. Society has been much more willing to limit individual freedom in the service of protecting people from certain communicable diseases (through mandatory vaccinations, for example) than from equally serious genetic diseases. This difference occurs in part because the likelihood of transmission is often less certain in the case of genetic disease and because genetic transmission occurs within the family, rather than the public at large. But more fundamentally, it reflects the facts that the prevention of genetic disease can impinge on reproductive freedom and that modern means of genetic screening developed just as this freedom was receiving

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<sup>10</sup> See, e.g., Kenneth M. Ludmerer, *GENETICS AND AMERICAN SOCIETY*, Johns Hopkins Univ. Press, Baltimore (1972).

increasingly explicit and extensive protection as a facet of a constitutional "right of privacy."<sup>11</sup>

For genetic screening and counseling to contribute to the public health goals of reducing the incidence and impact of inherited disorders, however, a subtle tension must arise between those goals and the special place accorded to the right of individuals to obtain and use screening information as their personal values dictate, whether or not their decisions result in a reduction in genetic disease.<sup>12</sup> While acknowledging the need for some balancing with public health goals, **the Commission strongly endorses the emphasis on genetic screening and counseling as medical interventions to be elected by an individual who desires information to aid in making personal medical and reproductive choices.**

*Contradictory pressures on the use of genetic services.*

Decisions about whether and how to use genetic services are not made in a vacuum. If voluntariness is to be maintained, therefore, attention must be paid to the pressures exerted by social attitudes as well as by official limitations regarding policies that bear on decisions about genetic diseases. At the moment, reproductive decisions involving genetic information are subject to pressures from opposite poles.

On the one hand, efforts have been made to limit genetic services because certain uses of genetic information are deemed unacceptable.<sup>13</sup> For example, some couples may find themselves faced with the difficult decision of whether to forego natural conception or to terminate a pregnancy. Yet screening results may also prompt a couple to prepare specialized medical or surgical treatment for an expected child; and screening information is more likely in the future to facilitate the intrauterine treatment of disorders.<sup>14</sup> Moreover, for most couples genetic screening (particularly prenatal diagnosis) and

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<sup>11</sup> See Laurence H. Tribe, *AMERICAN CONSTITUTIONAL LAW*, Foundation Press, Mineola, N.Y. (1978) at 886-990. See also, Ludmerer, *supra* note 10.

<sup>12</sup> This tension is also reflected in some aspects of the debate over directive and nondirective counseling. For a further discussion, see pp. 36-38 *supra*.

<sup>13</sup> The March of Dimes, for example, has been a target of some anti-abortionists because of the organization's support for genetic services. See, e.g., Fr. John Dietzen, *Question Box*, *CATHOLIC STANDARD*, Jan. 22, 1981, at 36; *Dr. Wilkie Says March of Dimes Hasn't Totally Reformed*, *NATIONAL RIGHT TO LIFE NEWS*, April 1978, at 3.

<sup>14</sup> If the capacity to perform prenatal therapy expands, significant changes are likely to occur in social expectations about parental and societal obligations toward the unborn. The fetus becomes a patient, rather than the inaccessible and largely unknown predecessor of an infant. One aspect of this change would be more-demanding social expectations of parents in promoting the welfare of the fetus. So although developments in prenatal therapy increase the range of

counseling relieve fears of transmitting certain serious diseases to their offspring. Indeed, the vast majority of women undergoing amniocentesis receive that reassurance; prenatal screening has facilitated the birth of at least hundreds of children who, but for the test, might never have been born.<sup>15</sup> **In sum, the fundamental value of genetic screening and counseling is their ability to enhance the opportunities for individuals to obtain information about their personal health and child-bearing risks and to make autonomous and noncoerced choices based on that information.** Abridgement of that autonomy—explicitly or implicitly—would diminish the value of genetic screening and counseling and undermine the achievement of their goals. Efforts to inform the public about genetic screening and counseling, and to ensure services for those who wish to participate, promote such autonomous decisionmaking.

On the other hand, parents who fail to take advantage of prenatal diagnosis and who bear a child with an “avoidable” disease may consider themselves—or may be considered by others—to be “responsible” for the disease in a way that contradicts the older notion that genetic diseases are solely a matter of fate for which individuals are not responsible.<sup>16</sup> Fear has been expressed about societal disapproval translating into a negative attitude toward such children, including an unwillingness to allocate adequate resources for their care or for research into the causes and prevention of their diseases.<sup>17</sup> Such a response would be indefensible; the claims of a handicapped child on societal resources should not be dependent on the decision of the child’s parents to undergo screen-

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technically feasible options, social pressures may severely limit parents’ freedom to refrain from choosing certain options.

<sup>15</sup> See, e.g., *Genetic Testing Imperfect but Is Still Valuable*, OB-GYN NEWS, Feb. 15-28, 1982, at 1; Aubrey Milunsky, *Medico-Legal Issues in Prenatal Diagnosis*, in Aubrey Milunsky and George J. Annas, eds., *GENETICS AND THE LAW*, Plenum Press, New York (1970) at 53.

<sup>16</sup> The directors of a thalassemia screening program in Great Britain report that

The existence of antenatal diagnosis has made things worse for couples of heterozygotes who are “missed”...and so produce a thalassaemic child. They now find the disease and its treatment much harder to accept than was formerly the case. Three out of five such couples known to us...express(ed) their conviction that once prevention methods are available, the continuing birth of affected children has become *someone’s* responsibility.

B. Modell *et al.*, *Population Screening for Carriers of Recessively Inherited Disorders* (Letter), 2 LANCET 806 (1980).

<sup>17</sup> See e.g., Arno G. Motulsky and Jeffrey Murray, *Will Prenatal Diagnosis with Selective Abortion Affect Society’s Attitude toward the Handicapped?*, in K. Berg, ed., *RESEARCH ETHICS*, Alan R. Liss, Inc., New York (in press).

ing. Such a response would also be out of keeping with current efforts to assure rights and opportunities for the handicapped.

The silence of the law on many areas of individual choice reflects the value this country places on pluralism. Nowhere is the need for freedom to pursue divergent conceptions of the good more deeply felt than in decisions concerning reproduction. It would be a cruel irony, therefore, if technological advances undertaken in the name of providing information to expand the range of individual choice resulted in unanticipated social pressures to pursue a particular course of action. Someone who feels compelled to undergo screening or to make particular reproductive choices at the urging of health care professionals or others or as a result of implicit social pressure is deprived of the choice-enhancing benefits of the new advances. **The Commission recommends that those who counsel patients and those who educate the public about genetics should not only emphasize the importance of preserving choice but also do their utmost to safeguard the choices of those they serve.**

*The special case of sex selection.* Despite the strong reasons for not precluding individuals from having access to genetic services on the basis of what they may do with the information, society may sometimes be warranted in discouraging certain uses. A striking example would be the use of prenatal diagnosis solely to determine the sex of the fetus and to abort a fetus of the unwanted sex.

Denying a woman access to the service for this purpose is sometimes defended on the ground of resource scarcity, since being the "wrong sex" is not a disease or even a condition that merits the limited time and facilities of genetic programs, as would conditions generally classified as genetic diseases. Nevertheless, parents bent on learning the sex of the fetus can probably do so, either by having another, acceptable reason for prenatal screening or by inventing one (such as claiming that the woman is over 35 years old).<sup>18</sup> The ethical concern about using knowledge of fetal sex as the reason for terminating a pregnancy thus goes beyond the resource issue, since even if resources were not scarce, the question of whether this is an acceptable ground for medical intervention would remain.

In a society in which women terminate pregnancies for a wide variety of reasons, it might seem indefensible to exclude sex selection, as a matter of public policy, or even to make it an object of informal social disapproval. As already noted, the Commission generally believes that medical options ought to be enhanced, not diminished. In the Commission's view, how-

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<sup>18</sup> Even those prospective parents who do not start off with a particular desire to know the sex of their fetus may learn it as a routine part of the process, although not everyone chooses to learn this information when its disclosure is offered.

ever, the question of sex selection raises special moral problems apart from the general issue of the morality of abortion. The willingness to undergo in the second trimester of pregnancy an invasive procedure that entails a risk of maternal morbidity as well as fetal morbidity and mortality, and perhaps to terminate a pregnancy intentionally, merely in order to satisfy a preference for choosing the sex of a child, calls into questions the values underlying such a decision.

There are several reasons that using amniocentesis and abortion for this purpose is morally suspect. In some cases, the prospective parents' desire to undertake the procedures is an expression of sex prejudice. Such attitudes are an affront to the notion of human equality and are especially inappropriate in a society struggling to rid itself of a heritage of such prejudices. There is no evidence that amniocentesis is being sought widely to determine fetal sex.<sup>19</sup> Surveys of parents and prospective parents do indicate, however, a preference for sons (especially as the first-born child).<sup>20</sup> If it became an accepted practice, the selection of sons in preference to daughters would be yet another means of assigning greater social value to one sex over the other and of perpetuating the historical discrimination against women. Of course, in some instances the judgment may be relative rather than absolute (for example, a couple with several girls who want a boy to complete their family) and in some instances the preference may be for a daughter rather than a son.

Another issue in sex selection is that parental concern with the sex of the fetus (to the point of aborting one of the undesired sex) seems incompatible with the attitude of virtually unconditional acceptance that developmental psychologists have found to be essential to successful parenting. For the good of all children, society's efforts should go into promoting the acceptance of each individual—with his or her particular strengths and weaknesses—rather than reinforcing the negative attitudes that lead to rejection.

The idea that it is morally permissible to terminate pregnancy simply on the ground that a fetus of that sex is

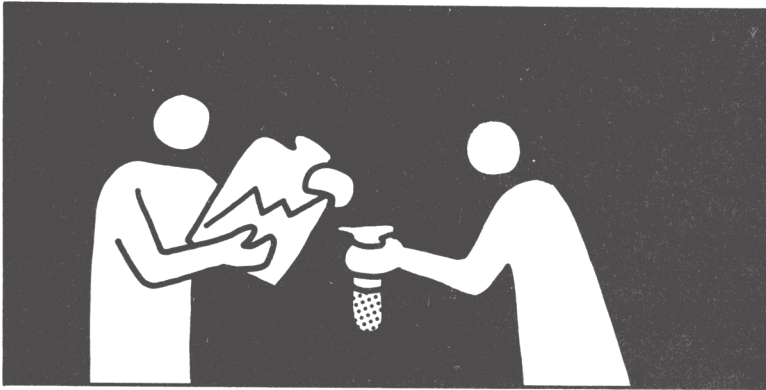
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<sup>19</sup> For example, one genetics center that has a publicized policy of performing amniocentesis for sex selection if, after counseling, the client requests it, reports only one request for this purpose in the six months since the policy was initiated. Haig H. Kazazian, *Prenatal Diagnosis for Sex Choice: A Medical View*, 10 HASTINGS CTR. REP. 17 (Feb. 1980). The author notes, "Our overall experience during the past eight years leads us to believe that couples desiring sex selection who are willing to undergo midtrimester abortions are uncommon in American society." It is unclear how frequently unplanned pregnancies are terminated because parents do not want to take a chance that the infant is of the unwanted sex.

<sup>20</sup> Amitai Etzioni, *GENETIC FIX*, Macmillian Publishing Co., Inc., New York (1973) at 227-28.

unwanted may also rest on the very dubious notion that virtually any characteristic of an expected child is an appropriate object of appraisal and selection. Taken to an extreme, this attitude treats a child as an artifact and the reproductive process as a chance to design and produce human beings according to parental standards of excellence, which over time are transformed into collective standards.

Although every reproductive decision based on information gained from genetic screening involves the conscious acceptance of certain characteristics and the rejection of others, a distinction can be made between seeking genetic information in order to correct or avoid unambiguous disabilities or to improve the well-being of a fetus, and seeking such information merely to satisfy parental preferences that are not only idiosyncratic but also unrelated to the good of the fetus.



Although in some cases it will be difficult to draw a clear line between these two types of interventions, sex selection appears to fall in the latter class. This is not to say that every decision to undergo amniocentesis solely for purposes of sex selection is subject to moral criticism. Nonetheless, widespread use of amniocentesis for sex selection would be a matter of serious moral concern. Therefore, **the Commission concludes that although individual physicians are free to follow the dictates of conscience, public policy should discourage the use of amniocentesis for sex selection.** The Commission recognizes, however, that a legal prohibition would probably be ineffective<sup>21</sup> and, worse, offensive to important social values (because vigorous enforcement of any such statute might depend on coercive state inquiries into private motivations).

<sup>21</sup> Deception by patients would be easy, even if physicians fully endorsed such a statute. Even if a law prohibited reporting of fetal gender until very late in the pregnancy, enforcement would be difficult.



Once new genetic technologies are in wide use, the emergence of new social norms about their proper use, and any corresponding limitations on individual choice, may be difficult or impossible to control. This is all the more reason to ensure that decisions to make available new uses of genetic services—such as sex selection—are guided by a serious effort to anticipate the moral implications of the subtle interplay of individual choices and the social norms they create and by which they are shaped.

## Knowledge

Genetic screening and counseling have the same central purpose: to make people into informed decisionmakers about their genetic constitution, to the extent it is relevant to choices about their own well-being or that of their family. Thus providing information in a way the participant can understand would plainly seem to be a goal of any genetics program and would also seem more likely if there is appropriate education of the public and of health professionals about current genetic knowledge. A commitment to disseminate information does not require policymakers or practitioners to ignore other values, such as well-being, confidentiality, or equity.

**Disclosure of Incidental Findings.** A genetic screening test undertaken to detect a particular genetic condition sometimes uncovers other information that could be very traumatic to the screenee. Genetic counselors and providers must decide whether such incidental information should be revealed to the individuals screened and, if so, how to reveal it.

**Findings of nonpaternity.** The finding that the putative father of a child is unlikely to be the biological father may arise during several types of medical screening. Screening family members to locate a suitable organ or bone marrow donor, for example, can incidentally yield strong evidence of nonpaternity. In these cases, however, the finding of nonpaternity has no bearing on personal medical decisionmaking (although it indirectly affects medical management, in that half-siblings and putative fathers may be excluded as donors because of an inadequate tissue match). Consequently, controversy has not arisen about the customary practice of not mentioning the possibility of nonpaternity to the potential organ donors. Findings of nonpaternity in the context of reproductive screening and counseling, however, present problems that are not so easily dismissed. The decisions based upon such screening and counseling rest on knowledge of the genetic makeup of the biological father. When doubts about paternity arise, therefore, they have direct ramifications for the counseling and decision-making process.

Following the birth of an affected child, parents often seek genetic counseling to know the likelihood that a subsequent child will also have the disease. If a carrier test for the disorder is available and has not already been done, this would be one way for the parents to obtain the information. If the condition in question is autosomal recessive, such as sickle-cell trait or Tay-Sachs disease, and the father is shown not to be a carrier, there is strong evidence of nonpaternity. Although explanations such as a spontaneous mutation, laboratory error, or even a mixup of newborns at the hospital could conceivably account for the unanticipated outcome, such occurrences are very rare. Genetic counselors have several choices for dealing with suspicions of nonpaternity.

First, they might choose not to inform the couple of the actual recurrence risk (the “bottom line”) in order to shield them from information that the father was not a carrier. The actual risk of bearing a child with the disease with only one carrier parent is typically near zero (that is, dependent only on the mutation rate); the risk if the father were a carrier would be 25%. The harm of this deception is that the couple may make inappropriate decisions about future childbearing based on inaccurate information. If the couple mistakenly believes they are both carriers and therefore have a 25% chance of bearing another affected child, they may try artificial insemination or decide to forego future pregnancies; if they conceived another child they might needlessly incur the risk and expense of prenatal diagnosis; or they might divorce and perhaps each seek noncarrier mates. (Of course, if the woman suspected that another man fathered the child, she might separately seek additional information about recurrence risks and not pursue any of these options.)

Second, counselors could convey the actual risk but withhold information about genetic transmission that would explain the reason for the risk and raise the suspicion of nonpaternity. There is no way for counselors to prevent a couple (or either partner) from obtaining such information from another source, however; the chance of this happening is increased if the attempt at deception leaves the couple feeling confused and anxious.

Third, spontaneous mutation could be presented as the explanation for the outcome, without suggesting any other reasons. Although less likely than the second deception to be a goad to independent inquiry, this strategy is also vulnerable to being overturned by outside sources of information that could indicate the infrequency of spontaneous mutations compared with nonpaternity. Fourth, nondisclosure might be a matter not of what is revealed, but to whom: the counselors could discuss the situation with the woman (who would probably suspect nonpaternity) without the putative father being present. Final-

ly, the counselors might disclose their findings, including the conclusion that recurrence risk in any future pregnancy with the putative father is virtually nil because the child is almost certainly illegitimate.

None of the alternatives that rely on incomplete or inaccurate information are fully compatible with genetic counselors' basic role as information-givers. The fourth approach involves partial disclosure, but excluding the putative father might make counselors feel they have become a party to the woman's intentional deception. Yet they may feel this is justified when they have reason to fear that the family or some of its members will suffer greater physical or psychological harm from disclosure of the suspicion of nonpaternity. One cogent argument against this line of reasoning is that the deception will often not succeed for long and that any hope the counselors have of supporting the family unit over the long term (and, in particular, in maximizing the child's prospects for well-being) may be seriously jeopardized by their deception of one or both parents.

The ethical argument against nondisclosure goes beyond these practical considerations. Although the possibility of nonpaternity may not necessarily arise during genetic counseling, counselors would seem to have an obligation to both partners counseled. Certainly, if the man were to *ask* about the possibility of nonpaternity, it is difficult to maintain that the counselors ought to withhold the information they have unless disclosure would probably result in a serious and irreversible harm (for example, a life-threatening attack by a husband on his wife). Even then, the obligation would seem to be to provide adequate protection for the parties at risk and then to disclose the information to the man in a way that minimizes the harm to him and the risk to others.

A basically different approach would be to inform all couples, prior to a test, that nonpaternity may be discovered. Knowing this possibility, screenees could agree with the counselors in advance on the particular way the information will be handled; if a genetics center has a firm policy on disclosure that is not satisfactory to a couple, they could go elsewhere for their screening. Although this approach has the advantage of involving couples in the decision about disclosure, it may also unnecessarily provoke sensitive, sometimes harmful, discussions and could discourage some women who would like genetic information from participating in screening.

**No strategy for addressing the sensitive issue of nonpaternity entirely avoids conflicts among professional goals and social norms and expectations. Full disclosure, combined with careful counseling that goes well beyond information-giving, would seem most likely to fulfill the principles of autonomy and beneficence. When circumstance preclude this, however,**

**an approach that accurately provides information on the genetic risk, even when the individuals counseled are sometimes left with an incomplete understanding of the reasons, is generally preferable.**

*Sex chromosome abnormalities.* Chromosomal studies sometimes uncover aberrations in the sex chromosomes. In a few rare cases, for example, instead of having the normal XX (female) or XY (male) pair of chromosomes, individuals have XO, XXY, or other abnormal combination. Some such disorders are associated with obvious physical or mental abnormalities; in other cases research is only beginning to provide data on the significance of the disorder in areas such as developmental effects and learning disabilities. When information about a sex chromosome aberration is disclosed to a patient or parent (particularly a prospective parent), it is important that any discussion of the limitations in present knowledge about the effects of the condition be made clear.

One incidental finding of genetic screening that raises especially sensitive issues concerning disclosure is the so-called XY-female, or testicular feminization syndrome. These individuals possess the chromosomal configuration of a male and undeveloped, undescended testes rather than female reproductive organs, yet they have all the secondary sexual characteristics of normal (XX) females.

Patients need to be informed of this finding for two important reasons. First, sterility is one feature of the XY-female condition, which could make a difference in an individual's life plan. Second, the accepted medical response to the condition is removal of the undeveloped gonads, since they pose a risk of cancer; this operation, like any other, requires the informed consent of the competent patient. Disclosure of the diagnosis here, as elsewhere, does not flow from any single-minded commitment to truth-telling for its own sake, without regard for its consequences, but rather serves the two values that underlie the requirement of informed consent generally: concern for patient well-being and respect for patient self-determination. Some practitioners, however, express grave doubts about the wisdom of full disclosure in such cases, stating that it would inflict unconscionable psychological harm to tell an unsuspecting patient that she is really a male.

Although the Commission appreciates the extreme sensitivity of this situation, it does not believe there are only two alternatives: deception through nondisclosure or a blunt, psychologically threatening revelation. Indeed, given that the concept of being a male (or a female) is in part biological and in part social and that even the purely biological concept is complex and multidimensional, it would be not only unneces-

sarily destructive but also misleading to tell an XY-female that she is mistaken about her sexual identity.<sup>22</sup> Instead, it might be more appropriate to convey to a patient the basic facts, which are relevant to decisions she must make, and elaborate further only in response to the patient's questions. How the information is presented depends, of course, on the patient's level of education and knowledge of human biology, but basically the person needs to be told that she did not develop a uterus and ovaries (and hence cannot bear children) and has nonfunctioning reproductive tissue that must be surgically removed in order to avoid a risk of cancer. The context in which the disclosure is made will be just as important as the choice of an accurate but sensitive way of expressing the needed information. As the Commission emphasized in its report *Making Health Care Decisions*, a sound relationship between patient and practitioner requires a continuing process of open communication, mutual trust, and a sensitivity to the particular values and needs of the patient.

**Public and Professional Education.** People are not only patients whose informed consent is required for particular genetic services but also responsible citizens participating in the broader process by which policy decisions are made. To function effectively in either role they need to be well informed about the nature and value of genetic screening and counseling in the context of health care and public health programs.

The doctrine of informed consent has been examined by many scholars and practitioners from law, medicine, philosophy, and the social sciences. The Commission's own report on the subject, in line with the prevailing view, concluded that the goal of patient-provider interactions is a process of shared decisionmaking involving an informed patient and a conscientious health care provider. This reasoning applies with particular force to genetic screening and counseling in the context of health care and reproduction. In the setting of mass screening programs, the same ethical norms of information and consent apply. Prior education in some of the basic principles of genetics would enhance people's ability to interpret the information conveyed about particular genetic procedures, and thereby facilitate true informed consent.

Furthermore, the formulation of public policy about matters of health should not be the exclusive prerogative of a small group of medical or public health "experts." Active and informed political participation by people without specialized training in the fields of medicine and human genetics is needed if the public interest is to be effectively represented. Conse-

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<sup>22</sup> DORLAND'S MEDICAL DICTIONARY, for example, includes psychological, social, and morphological as well as chromosomal definitions of "sex."

quently, educational efforts should consist of more than just informing individual patients about specific medical genetic procedures.

Adequate professional education is also necessary for genetic screening and counseling to become accepted components of public health efforts and standard medical care. Physicians across a broad range of specialties must be knowledgeable about the detection and treatment of genetic disease if patients are to receive the most beneficial care. Studies show, for example, that about 30% of the children in pediatric hospitals have diseases with either a clearly genetic or multifactorial etiology.<sup>23</sup> Continuing professional education is essential if the potential of new advances in the diagnosis and treatment of genetic diseases is to be realized. Several recent judicial decisions have recognized the importance of genetics in medical care; the courts have held physicians liable for failing to inform patients of their risks for genetic disease and of the availability of screening tests.<sup>24</sup> To be alert to these genetic risks, physicians need to increase their knowledge in this field.

**Public education on basic genetic concepts.** Most people do not have an educational background in the modern concepts of human genetics, particularly concerning human genetic disorders,<sup>25</sup> and this has been shown to be a barrier to effective genetic counseling.<sup>26</sup> A committee of the National Academy of Sciences concluded that "it is essential to begin the study of human biology, including genetics and probability, in primary school, continuing with a more health-related curriculum in secondary school."<sup>27</sup> By teaching young children the concepts of human variability, genetics education can dispel unfounded fears and help people understand and respond appropriately to genetic differences among groups.

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<sup>23</sup> Judith G. Hall *et al.*, *The Frequency and Financial Burden of Genetic Disease in a Pediatric Hospital*, 1 AM. J. MED. GENETICS 417 (1978).

<sup>24</sup> *Turpin v. Sortini*, 31 Cal.3d 220, 643 P.2d 954 (1982); *Becker v. Schwartz*, 46 N.Y.2d 401, 386 N.E.2d 807 (1978); *Howard v. Lecher*, 42 N.Y.2d 109, 366 N.E.2d 64 (1977). *See also*, Ellen Wright, *Father and Mother Know Best: Defining the Liability of Physicians for Inadequate Genetic Counseling*, 87 YALE L.J. 1488 (1978); Capron, *supra* note 6.

<sup>25</sup> Biological Sciences Curriculum Study, *Guidelines for Educational Priorities and Curricular Innovations in Human and Medical Genetics*, 1 BSCS JOURNAL 20, 28 (1978).

<sup>26</sup> Clare O. Leonard, Gary A. Chase, and Barton Childs, *Genetic Counseling: A Consumer's View* (Special Article) 287 NEW ENG. J. MED. 433, 438 (1972).

<sup>27</sup> Committee for the Study of Inborn Errors of Metabolism, *GENETIC SCREENING: PROGRAMS, PRINCIPLES, AND RESEARCH*, National Academy of Sciences, Washington (1975) at 3.

The importance of early education in genetics was also underscored by the Biological Sciences Curriculum Study (BSCS):

Because the study of human genetics is not exclusively a biological science, and because most of its content deals with values, feelings, and emotion, it is important to provide information on this subject to children at a time when their fundamental attitudes are being formed.<sup>28</sup>

The educational approaches should recognize that information on genetics sometimes raises troubling and sensitive issues for certain individuals and groups. People at increased risk for a disease or of being a carrier may fear or actually encounter stigmatization or may experience a loss of self-esteem. Material on genetic disease should be presented in a way that does not inappropriately and insensitively single out particular groups.

The BSCS represents an important effort to redress deficiencies in primary and secondary school genetics education. **The Commission commends efforts to develop curricula and to work with educators to incorporate genetics material in the classroom. The knowledge imparted is not only important as a basic part of science education but also promotes values of autonomy and informed public participation.**

The field of genetics is rapidly changing; even people who gain a sound knowledge of basic genetic principles while at school will need continuing sources of information. Groups like the March of Dimes and associations concerned with specific diseases, such as the Cystic Fibrosis Foundation and the National Committee to Combat Huntington's Disease, can play an important part in this public education effort. Their programs to prepare people to be autonomous decisionmakers and informed participants in the formation of policy on genetics deserve encouragement and support. The Commission also encourages individual genetics professionals to teach school and community groups and to write articles for general-circulation magazines and newspapers.

**Professional education.** Deficiencies in genetics education extend to the curriculum for many health professionals. Except for programs that specifically provide training for medical geneticists and nonphysician genetic counselors, human genetics is not uniformly taught in schools of medicine, nursing, and the other health professions. A report on medical school curricula found that 30% of the 104 medical schools studied offered no formal education in genetics.<sup>29</sup> The 70% that did

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<sup>28</sup> *Guidelines for Education Priorities and Curricular Innovations in Human and Medical Genetics*, *supra* note 25, at 21.

<sup>29</sup> Barton Childs *et al.*, *Human Genetics Teaching in U.S. Medical Schools*, 33 AM. J. HUMAN GENETICS 1 (1981).

provide training in genetics devoted varying degrees of emphasis to the subject. The paucity of medical school training was evident in National Board of Medical Examiners' scores: the ability to answer questions on medical genetics varied directly with the number of hours of training received in medical school. **The Commission encourages the Association of American Medical Colleges and professional societies, such as the American Medical Association (AMA) and the American Nursing Association, to upgrade genetics education for professional students.**

Postgraduate education is also important to make professionals aware of new developments in genetics and several organizations have promoted continuing education. The Council on Scientific Affairs of the AMA, for example, recently encouraged medical specialty societies to expand their efforts to train physicians in the newer techniques of prenatal diagnosis.<sup>30</sup> The Federal government and the March of Dimes sponsor fellowships to train medical geneticists. Blue Cross/Blue Shield of New York and the National Genetics Foundation operate a toll-free "hotline" for physicians seeking information on genetic disease<sup>31</sup>; the enthusiastic response to the service attests to professional interest in up-to-date genetic information. Continuing education is important not only for physicians, but also for health educators, genetic counselors, and others involved in the delivery of genetic information and services. **Organizations like the March of Dimes and governmental bodies make important contributions to this goal of professional education and therefore deserve public support. It is important that these educational efforts go beyond technical matters in genetic screening and counseling and include instruction about the role of informed consent, the psychosocial implications of screening and counseling, and the central place that value preferences hold in personal decisionmaking.**

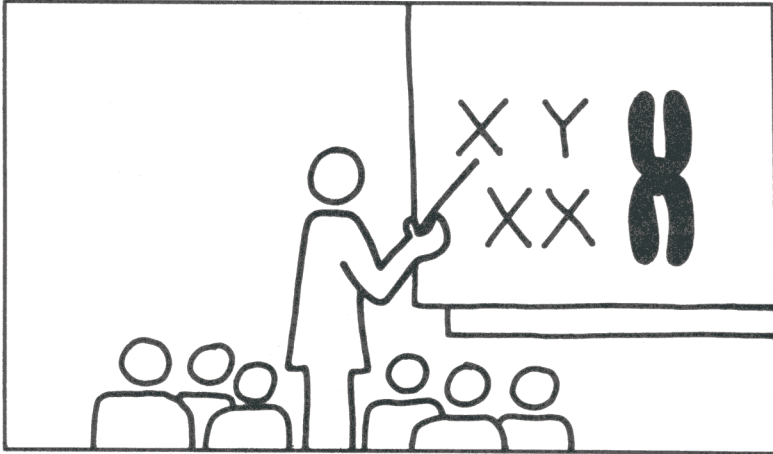
*Education for particular screening programs.* Improved public and professional education in human genetics generally can help set the stage for education on programs targeted at specific potential screening populations. Information should be aimed at both professionals and the public, drawing on past experience with screening programs and current expertise in health education. Prominent lay and professional communications media are important vehicles for widespread exposure about screening programs. Again, it is essential that the programs be sensitive to possible public misconceptions and to the risk of personal stigma that might occur when a certain subgroup is identified as at high risk for a deleterious genetic

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<sup>30</sup> Council on Scientific Affairs, *Council Report: Genetic Counseling and Prevention of Birth Defects*, 248 J.A.M.A. 221 (1982).

<sup>31</sup> *Genetics Hotline Established*, FAST FACTS FOR PHYSICIANS (Blue Cross/Blue Shield of Greater New York), April 1982, at 1.





condition. In light of the anxiety that can arise among candidates for screening, the way information about genetic diseases and tests is presented deserves careful attention.<sup>32</sup> Community leaders and organizations representing the population to be screened should play an integral part in program planning—without their involvement, a program is unlikely to be effective. Moreover, excluding such groups violates ideals of public participation and represents a paternalistic intervention that shows a lack of respect for individual and community autonomy.

Before launching a program, it is also important that all participating health care professionals are adequately educated about its purposes and procedures. As demonstrated by the study of physician education about AFP testing,<sup>33</sup> this can be a less straightforward task than might be assumed. Failure to educate professionals adequately could lead to poor-quality testing and counseling and result in serious harm to patients and their children. Professional education is thus a crucial link in the implementation of a screening program; it provides an essential ethical safeguard. Even professionals not directly involved in counseling or screening must be well informed if they are to be effective in referring individuals to the program and in responding to the concerns and questions of their patients. **Therefore, the Commission believes that it is essential for professional educators, working with specialty societies**

<sup>32</sup> For two views of psychosocial implications of public screening programs for Tay-Sachs disease, see Fred Massarik and Michael M. Kaback, *GENETIC DISEASE CONTROL: A SOCIAL PSYCHOLOGICAL APPROACH*, Sage Publications, Beverly Hills, Calif. (1981), and Madeleine J. Goodman and Lenn E. Goodman, *The Overselling of Genetic Anxiety*, 12 HASTINGS CTR. REP. 20 (Dec. 1982).

<sup>33</sup> See note 59, Chapter One *supra*.

**and program planners, to identify effective methods to educate professionals about new screening tests.**

## Well-Being

The promotion of personal well-being is a major objective underlying all the facets of health care considered by the Commission. This goal—sometimes stated as the principle of beneficence—has definite application in the field of genetics both for the work of individual health care professionals and for the decisionmaking of officials of public and private bodies.

**The Special Case of Artificial Insemination by Donor.** Almost 100 years after the first successful artificial insemination by donor (AID)<sup>34</sup> was performed in 1884, a host of legal, social, and ethical questions still surround the procedure. Although a comprehensive analysis of these issues is beyond the scope of this report, the Commission felt it was important to consider the role of genetic screening and counseling in AID.

Each year, an estimated 6000-10,000 infants are born in the United States as a result of AID. A recent study found that little, if any, information is obtained about the genetic history or genetic risks of the donor.<sup>35</sup> Moreover, recordkeeping on the source of semen samples is sparse.<sup>36</sup> This is largely due to a desire to provide donors with anonymity and protection against legal liability. However, this casual approach to obtaining donor samples poses several potentially serious problems.<sup>37</sup>

First, there is the risk of genetic disease in the offspring. Women who are Tay-Sachs or sickle-cell carriers, for example, might unknowingly receive sperm from another carrier and consequently bear a child with the condition. Similarly, serious problems could occur if a woman whose blood is Rh-negative is inseminated with sperm from a donor whose Rh factor has not been ascertained. Second, one effect of minimal record-

<sup>34</sup> Artificial insemination is classified into three types, based on the source of the semen: by husband (AIH); by donor (AID), in which the semen comes from a third party; and by husband and donor (AIDH), in which semen from the two sources is combined. The Commission's discussion applies to the last two categories.

<sup>35</sup> Martin Curie-Cohen, Lesleigh Luttrell, and Sander Shapiro, *Current Practice of Artificial Insemination by Donor in the United States*, 300 NEW ENG. J. MED. 585 (1979).

<sup>36</sup> F. Clarke Fraser and R. Allan Forse, *On Genetic Screening of Donors for Artificial Insemination*, 10 AM. J. MED. GENETICS 399 (1981).

<sup>37</sup> The same concerns about a donor's genetic contribution also apply when a woman donates an egg for an *in vitro* fertilization procedure or when sperm from the husband of an infertile woman is used to impregnate a woman (a surrogate mother) who gestates an infant who will be returned at birth to the man and his wife. These procedures are far less common in the United States at this time.

keeping is that when AID results in genetic disease, the source of the sample cannot be determined; semen from that donor may be used again and may result in another child with that disease. Indeed, the Commission heard testimony about just such a case, involving one woman who bore two children with the same serious genetic disorder.<sup>38</sup> Lack of recordkeeping also makes it impossible to alert the donor that any of his own offspring are at risk—information he might find useful for his plans about having children. Finally, there is the possibility that children conceived from the same donor (half-brothers and half-sisters) might marry. Children of such an unwittingly incestuous union would be at increased risk for rare genetic disorders. The likelihood of this occurring would probably be greatest if several individuals in a small town were inseminated with sperm from one donor.

As elaborated in the Commission's report *Making Health Care Decisions*, true informed consent in patient-provider relationships involves a discussion of the possible benefits and risks of a contemplated medical procedure and of the alternatives. Accordingly, a woman considering artificial insemination should be apprised of the risks being taken by conceiving a child with a donor's sample.<sup>39</sup> Clearly it is not feasible—or even possible—to enumerate the risk of the thousands of diseases of genetic origin. When a genetic history and genetic screening could provide useful data about the risks for particular diseases, however, this information is an important element of informed decisionmaking. For example, a black woman who is a sickle-cell carrier or a Jewish woman who carries a gene for Tay-Sachs disease should know the carrier status of the potential donor as part of her decisionmaking process; an Rh-negative woman should know the Rh status of the donor.<sup>40</sup> Women seeking AID are very eager to bear children. If no information is available on potential donors,

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<sup>38</sup> Testimony of Dr. Kurt Hirschhorn, transcript of the 18th meeting of the President's Commission (March 12, 1982) at 227.

<sup>39</sup> For example, recent data suggest that AID may be associated with an increased rate of birth defects. R. Allan Forse and F. Clarke Fraser, *Is AID Teratogenic?*, 34 AM. J. HUM. GENETICS 89A (1982). Further research in this area is needed to determine whether the process increases the likelihood of adverse germ-cell changes.

<sup>40</sup> The obligation of the physician who performs the insemination to provide genetic information on the donor can be compared to an obstetrician's responsibility to identify possible genetic risks in the prospective parents of a traditional union. For example, a doctor is expected to inform a Jewish woman who is pregnant or who is considering having a child about Tay-Sachs disease and the availability of screening tests for it. She and her husband would then have the option of obtaining carrier tests and, if appropriate, the prenatal test for Tay-Sachs. If the conception is going to occur with a third-party donor, the woman should likewise have the option of obtaining

they might nonetheless agree to the procedure. Providing them only with the options of inadequate information or no insemination is inconsistent with the values underlying informed consent.

**The Commission concludes that a genetic history should be obtained on all potential sperm donors and, where appropriate, the results of genetic screening should be available to prospective recipients with a view toward promulgating guidelines for those involved in obtaining samples and performing AID.** Professional associations, such as the American Society of Human Genetics or the American College of Obstetrics and Gynecology, are probably best suited to develop and disseminate such criteria.<sup>41</sup>

Policies on recordkeeping involve balancing confidentiality interests with the prevention of harm. To prevent harm to future offspring and families from repeated use of samples in unfavorable circumstances, records of the source of the sample should be kept. Harm might also be prevented if donors were informed about any risks of genetic disease that were identified during the screening.

Recordkeeping does pose a potential risk that a paternity suit might be initiated, that a child might wish to locate his or her biological father, or that a donor might seek out his offspring. **The Commission believes that safeguards could be put in place to minimize the risk that recordkeeping would violate confidentiality interests. Law reform groups, as part of a much-needed reformulation of law in this field, should include provisions that will allow the source of donor samples to be identified and the results of genetic tests to be recorded in a way that protects the confidentiality of the donor to the greatest extent possible.**

The chance of unwittingly incestuous marriages can best be reduced if physicians take care to use samples from a variety of donors when inseminating women in one particular locale. This, of course, presumes that it is possible to determine that the source of the samples is different, a concern that should be addressed by the recordkeeping system recommended.

**Ensuring Accuracy and Safety of All Programs.** The value of genetic screening lies in providing information that can assist people in making voluntary decisions about health care and reproduction that reflect their personal values. This

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information about the chances of bearing a Tay-Sachs child; this is possible only if information on the carrier status of the donor is available.

<sup>41</sup> Fraser and Forse, *supra* note 36, recently proposed a set of guidelines for donors that could serve as a starting point for general consideration.

information can have an enormous impact on the physical and emotional well-being of patients and of prospective parents and their children. Failure to provide accurate information not only thwarts the potential benefits of screening but can cause harm.

***Pilot programs.*** Pilot studies are an essential means of determining the accuracy and reliability of a test before it is introduced to the general population. **Public screening programs should not be implemented until they have first demonstrated their value in well-conducted pilot studies. The Food and Drug Administration (FDA) and other relevant government agencies should require such studies as a prerequisite to introducing new products for general use.** These studies should yield information on the false positive and false negative rates associated with possible cutoff points and on the predictive power of the test in the populations to be screened. Ultimately, individual physicians and an informed public can act as the final check on the system by requiring that a test's value be established before they participate in a screening program.

Although pilot studies should precede the introduction of a screening test into the health care system, it is not clear who bears the responsibility for producing the data and funding the studies. If FDA classifies a test as a class III medical device, proof of its safety and efficacy is required before it is marketed.<sup>42</sup> In these cases, the companies seeking to market the product must provide FDA with data from human subjects research. Experience with AFP test kits, however, demonstrated a confusion about the extent and nature of the studies that commercial companies must provide and about the safety and efficacy standard that should be applied to genetic screening tests.<sup>43</sup> With these issues still unresolved and with other tests likely to raise similar questions, **the parties involved—including regulators, funding agency administrators, industry representatives, researchers, and public health officials—should meet to discuss their respective roles in ensuring that a prospective test is studied adequately before genetic screening programs are introduced.**

***Monitoring long-term outcome.*** In addition to careful design and proper pilot studies, an evaluation of the long-term effects of genetic screening is important. Such monitoring may be necessary if the low-frequency adverse effects of screening are to be detected, since pilot studies involve only a limited

<sup>42</sup> The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act establish three categories of medical devices for regulatory purposes—those requiring (1) general controls; (2) performance standards and (3) premarket approval. 21 U.S.C. § 360c (a)(1)(1976).

<sup>43</sup> David Dickson, *Alpha Fetoprotein: Too Hot to Handle?*, 280 NATURE 6 (1979). See also p. 29 *supra*.

population. A small but significant error rate, for example, may not become evident until a larger population undergoes the test. Some effects—both physical and psychosocial—may be so unanticipated that the initial evaluation procedures overlook them; other effects may not be manifested until after the pilot study.

Information about the medical and psychological consequences of screening gained from extended follow-up enhances the informed consent process and the overall determination of the risks and benefits of a program. Despite this value, follow-up research is too often neglected. This is in part due to the methodological difficulties and expense of following or locating screening participants, sometimes several years after they took part in the program. Federal funding for follow-up studies has been sparse. Research on stigmatization and other possible psychosocial effects of screening has for the most part been seriously inadequate. **The Commission finds that if ethical and policy goals are to be promoted, every screening program should have an evaluation component.** In some cases it may not be possible or even necessary to conduct extensive follow-up research, but needs of each particular program should be considered. Sometimes the scope of the studies, the significance for potential screenees throughout the country, and the involvement of programs in several states make this evaluation an appropriate function of the Federal government. However, officials administering more-limited programs should also be aware of the needs for long-term monitoring. In addition, follow-up of participants by a genetic counselor can provide a valuable service.

*Professional and quality standards.* Adapting a successful experimental procedure to wide-scale use often requires more than merely enlarging its scope. A broadly based pilot study provides important data on the effects of a genetic test, but it still benefits from the special preparation that health professionals, laboratory facilities, and others make for an experiment. Proper research, by definition, involves a carefully controlled situation. The real world is less ideal, and therein lie serious ethical and policy issues for those who initiate new screening efforts.

Questions both of quality and of quantity arise. The quality questions concern the ability of those in a genetic screening program to meet a necessary standard of performance. Laboratories are a prime focus of this concern. It is unrealistic to expect that laboratory errors can be avoided entirely. Samples can be labeled incorrectly, clerical mistakes can be made in reporting results, and other such “human errors” can occur. With well-trained, conscientious professionals, however, these should be very rare.

Another source of error relates to the diffusion of a new screening technology. Widespread use of a new screening technique can attract a large number of laboratories anticipating commercial advantages from the test and seeking to enlarge access to it in their locale. Yet some of them may serve a small population or a population with a low incidence of the disease; these laboratories will probably never gain extensive experience performing the test. Cases of PKU are less likely to be missed when tests are conducted by a more-skilled, centralized laboratory that processes a large number of samples than when they are done in a smaller facility that receives fewer samples.<sup>44</sup> But if screening samples are not stable over time and distances, the effect of laboratory centralization may be to restrict access to screening programs to the areas of high population density served by these larger laboratories.

These are not easy conflicts to resolve. Yet the underlying ethical and policy goals promoted by screening are undermined by inaccurate results. **The Commission believes that screening should only be undertaken if results that are produced can be routinely relied upon.** Thus, specific mechanisms must be in place to preclude involvement of laboratories, physicians, or other elements of a program that fail to meet these standards. Federal licensure of interstate laboratories and proficiency testing are important quality-control measures. State agencies and professional associations such as the Joint Commission on Accreditation of Hospitals, the College of American Pathologists, and the American Board of Medical Genetics can also play important roles in promoting sound laboratory performance.

Laboratory quality-control measures are targeted toward each specific genetic test. Performance standards for providers and counselors participating in particular screening programs are a far less familiar notion, however. As already noted, educational programs and evaluations of their effectiveness are important adjuncts to general professional standards and licensure. Existing norms of tort liability may provide a means of redress to individuals injured as a result of negligence, but the Commission finds this after-the-fact approach to quality control inadequate. Indeed, fear of liability may work in conflicting ways; it may cause those involved in testing to be more cautious, but it could also prompt an ill-prepared provider to perform a test. This problem is not restricted to lack of technical proficiency. Physicians may possess the skill to withdraw amniotic fluid, for example, but not understand

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<sup>44</sup> David L. Meryash *et al.*, *Prospective Study of Early Neonatal Screening for Phenylketonuria*, 304 NEW ENG. J. MED. 294 (1981); Neil A. Holtzman *et al.*, *Screening for Phenylketonuria* (Letter), 304 NEW ENG. J. MED. 1300 (1981).

the meaning of various outcomes, or they may lack the time or expertise to counsel patients in a way that would provide some balance of benefits and harms and help patients make decisions based on the information.

Much of the responsibility for establishing and enforcing performance standards for a particular test will fall to the professions themselves. Nevertheless, public officials, including those who fund programs or regulate screening products, share responsibility for seeing that the test is used in a way that will maximize benefits and minimize harm.

When a screening test is promoted by a laboratory or offered independently by physicians rather than as part of a coordinated program, overall responsibility for coordinating and assessing its availability and quality may be overlooked. As one leading physician-geneticist told the Commission:

Most of the mistakes, most of the ethical transgressions, most of the failures to observe people's rights, most of the breaches of confidentiality and of informed consent and so on occurred early on when screening was being done by individual investigators or by interested lay groups, when it was being done in inappropriate places, and before the network of educators, counselors, physicians, health officers, and the like were set up.<sup>45</sup>

Some states have created bodies to oversee the execution and evaluation of genetic screening programs and to avert harm that can result when responsibility for coordinating programs is not clearly assigned. These organizations benefit from both public and professional input in policymaking.<sup>46</sup> **Such bodies can provide an important focus for the successful provision of genetic services. Other states could benefit from such an arrangement. In its absence, medical specialty groups, state and local health officials, or others must assume these important responsibilities.**

Requests for a new test can place demands not only on the performance quality of providers, but also on the quantity of adequate resources. Clearly these are related issues—demand that outstrips the capacity of qualified providers can prompt inadequately prepared groups to fill the gap. A genetic test performed or overseen by a physician is only one part of a network of prescreening and follow-up procedures and services. The unavailability of any part of this network can undermine the goals of a screening program. An inadequate laboratory capacity or roster of counselors to explain the test,

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<sup>45</sup> Testimony of Dr. Barton Childs, transcript of 9th meeting of the President's Commission (May 8, 1981) at 9.

<sup>46</sup> For a description of the Maryland Commission on Hereditary Disorders, see Neil A. Holtzman, *Public Participation in Genetic Policymaking*, in Aubrey Milunsky, ed., *GENETICS AND THE LAW II*, Plenum Press, New York (1980).



interpret test results, and discuss options or follow-up studies can render the information from an initial screening test more harmful than beneficial to the screenee. Therefore, **the Commission recommends that those who conduct or oversee screening programs ensure that the anticipated demand for the full range of services can be met before a test is offered.** Yet if this principle is applied to the existing system—in which some groups lack access (for geographical or financial reasons) to certain of the necessary services or options for medical management—then access to genetic screening and counseling ought not to be provided to some people. From the viewpoint of well-being, this result seems sensible because of the network of prescreening and follow-up services that an effective genetic screening program requires. If all the services are not available, it may seem unwise to perform screening.

Yet in ethical terms, applying the net benefit principle to a group that lacks access to the full range of health services associated with genetic screening doubles the detriment those people experience in the area of health services. If policymakers accept that a low-income population at risk for a genetic disorder will be unable to avail themselves of a full range of services or treatment options because of a lack of private funds and because the medical procedures in question are not covered by Medicaid, then it would seem that these people should be denied that screening service. Thus, problems of access to genetic screening and counseling are inextricably connected with ethical issues in access to health care in general and with the still larger issue of distributive justice. **When a screening program is needed but auxiliary services are unavailable, efforts to remedy resource limitations and improve access should be undertaken.**

## Equity

The concern that appropriate quality standards not leave already underserved populations without access to the genetics service that are made available to others has already pointed to the relevance to this field of a final ethical and legal concern—that of equity or fairness. In the context of highly sophisticated biomedical techniques, it is important to guard against the tendency to treat as matters of scientific expertise what are actually ethical decisions about the allocation of benefits and burdens.

**Distributing Benefits.** The availability of services sometimes depends on factors other than economic resources, race, or place of residence. In the area of genetic screening, for example, it is now common practice for physicians to offer amniocentesis for “advanced maternal age” only to women age 35 years or over. In effect, this is a policy about the way in which this beneficial service should be distributed.

The medical literature today invariably lists maternal age of 35 or over as an indication for prenatal diagnosis through amniocentesis because such women have an increased risk of bearing a child with a chromosomal defect.<sup>47</sup> The courts have reinforced this policy by accepting this standard, articulated by medical professionals as the measure of “due care”: that is, physicians who have failed to inform 35-year-old pregnant women about the availability of amniocentesis may be found negligent and therefore be held liable if a patient of theirs bears a child with such a defect.<sup>48</sup> A pregnant patient who is 34, however, may well not be told about amniocentesis or may even be told, if she asks for it, that the procedure is unavailable or inappropriate.

The policy of counseling only women age 35 or over about the benefits and risks of amniocentesis has been adopted informally by many practitioners over the past ten years.<sup>49</sup> The practice has been institutionalized by some laboratories that do not accept amniotic fluid samples from women under age 35 (in the absence of other risk factors).<sup>50</sup> This disparity illustrates the questions of fairness and equity that arise in genetic screening and counseling: in what way, and for what reasons, is it ethically acceptable to limit access to genetic services? An answer to that question in the context of amniocentesis must begin with an examination of the origin (in about 1968) of the age-based distinction and a review of whether the factors relied on then remain relevant today as the basis for an ethically acceptable policy.

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<sup>47</sup> A 1974 editorial in the *Journal of the American Medical Association*, for example, asserted that any pregnant patient more than 35 years old should have amniocentesis. Jack W. Pearson, *The Management of High-Risk Pregnancy* (Commentary), 229 *J.A.M.A.* 1439 (1974).

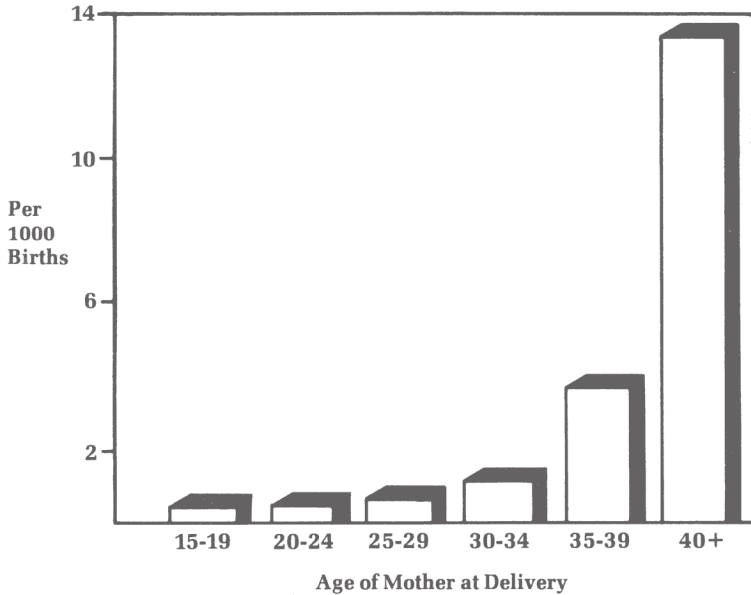
<sup>48</sup> *Werth v. Paroly*, No. 74025162NM (Wayne Co., Mich. Ct., verdict, Jan. 12, 1979); *Call v. Kezirian*, 185 Cal. Rptr. 103 (1982).

<sup>49</sup> The effect of this practice is to restrict access to the procedure to pregnant women older than 34. Younger women may be able to obtain the service if they pay for it. However, if they are not informed of its availability, if they must locate the service independently—sometimes with difficulty if restrictive state laboratories service the area—and if they must pay the full cost of several hundred dollars, then clearly they face significant barriers not encountered by older women.

<sup>50</sup> For example, the Prenatal Diagnosis Laboratory of New York City has a policy against conducting cytogenetic studies on fluid from women younger than 35 unless other risk factors are present. Information provided by personal communication with Dr. Lillian Hsu, Director, Prenatal Diagnosis Laboratory of New York City (1982). See also, Diana Paul, *Access to Amniocentesis* (Letter), 303 *NEW ENG. J. MED.* 1005 (1980) describing her efforts to obtain amniocentesis at age 30 “even though the state of California has an implicit policy of denying that procedure to women under 35 unless there is a family history of chromosomal disorders.”

**Figure 1: Prevalence of Down Syndrome by Age of Mother, in Five-Year Maternal Age Intervals, 1954-1965**

Source: Brian MacMahon and Thomas F. Pugh, EPIDEMIOLOGY: PRINCIPLES AND METHODS, Little, Brown and Company, Boston (1970) at 328.



Although there was no formal process from which the 35-year-old cutoff arose, several factors apparently led to it in the early days of the procedure. First, data on the relationship between maternal age and Down Syndrome were then collated in five-year age intervals and a marked increase in risk occurred in the 35-40 year age-group (see Figure 1). Second, the risks of amniocentesis to the mother and the fetus—subsequently found to be less than 1% morbidity and mortality—were then regarded as potentially serious. The unknown risk argued for limiting the procedure to those most likely to have an affected pregnancy, meaning that the probability of harm from the procedure was less likely to be disproportionate to the risk of bearing an affected child. Third, from a public health perspective, the greatest impact in reducing the incidence of Down Syndrome with the least expenditure (that is, the most cost-effective method) was to concentrate resources in the 35-and-over age-group. Data cited in a 1969 meeting showed that women 35 and over accounted for 13.5% of all births but about 50% of Down Syndrome births.<sup>51</sup> Thus, theoretically, the

<sup>51</sup> John W. Littlefield, *Introductory Remarks* (at conference on Down's Syndrome (Mongolism), Nov. 24-26, 1969), 171 ANN. N.Y. ACAD. SCI. 379 (1970).

incidence of the condition could be reduced significantly by screening this limited age-group. Finally, the specialized training, time, and expense required to analyze amniotic fluid samples assured that a significant start-up time would be required; the resource would be scarce, at least in the initial phases of the program, so some method for restricting access would be needed. The birth rate fell off markedly at age 34, making the group of women over that age a manageable one.

In light of these factors, concerns for fairness and equity argued in favor of concentrating resources on women who were at least 35. Moreover, since amniocentesis for prenatal diagnosis was initially a research procedure, it is not inappropriate that decisions about the selection of the population rested in the hands of the medical experts. However, each of these considerations is also subject to change over time. Sound decisionmaking calls for a process by which the policy can be reevaluated when changes occur in these or other factors that would alter the basis for the policy.

In fact, many of the factors have changed—or could be changed—in significant ways. Information is now available on the incidence of Down Syndrome by maternal age in single-year intervals. Whereas the five-year age-interval data showed a marked upward swing at age 35, the more detailed data show instead a steady increase in incidence with increasing age (see Figure 2). These data do not suggest the obvious cutoff point seen in the earlier chart.

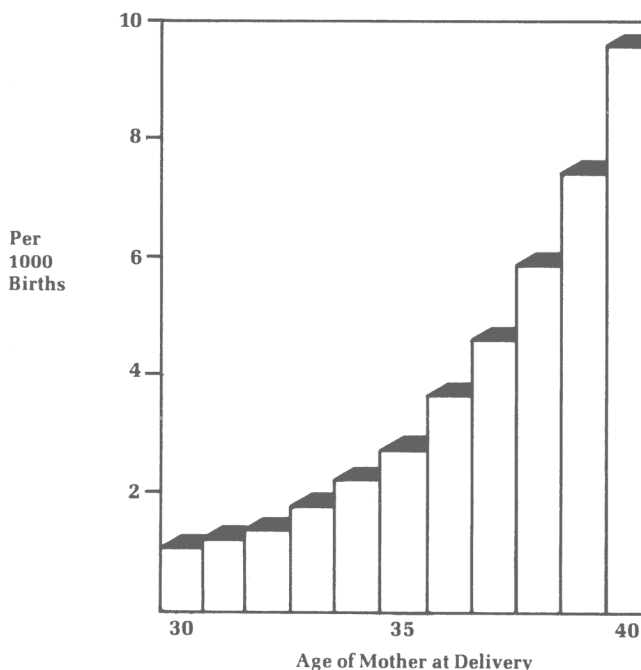
In addition, the demographics of the childbearing population have shifted significantly in the last two decades; the economic justification for the policy in 1970, which was based on data from the 1950s and 1960s, weakens in light of recent data. The proportion of all births to women age 35 or over dropped from about 10% in the 1960s to about 4.5% by the mid-1970s. This decrease resulted in the percentage of Down Syndrome births that are to older mothers declining from about 44% in 1960 to 21% in 1978.<sup>52</sup> This decline in the proportion of these births that are to older women reflects demographic shifts (that is, the larger proportion of all births to younger women), not the impact of prenatal diagnosis. Amniocentesis was in very limited use at the time the data were collected. Therefore, although older mothers are at the highest risk of bearing infants with chromosomal abnormalities, and although the procedure offers beneficial information to them, it no longer seems possible to achieve marked reductions in the incidence of Down Syndrome by focusing resources solely on this limited population of pregnant women.

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<sup>52</sup> Melissa M. Adams *et al.*, *Down's Syndrome: Recent Trends in the United States* (Special Communication), 246 J.A.M.A. 756 (1981); Lewis B. Holmes, *Genetic Counseling for the Older Pregnant Woman: New Data and Questions*, 298 NEW ENG. J. MED. 419 (1978).

**Figure 2: Prevalence of Down Syndrome for Mothers Aged 30-40, in Single-Year Intervals (New York), 1974**

Source: Derived from National Institute of Child Health and Human Development, ANTENATAL DIAGNOSIS: REPORT OF A CONSENSUS DEVELOPMENT CONFERENCE, Dept. of Health, Education, and Welfare, Washington (1979) at I-49.



Recent research has also injected another consideration into the assessment of risks for Down Syndrome births relative to maternal age. Studies have shown that in about 24% of the cases the extra chromosome 21, which is frequently characteristic of the condition, is contributed by the father.<sup>53</sup> Although it is possible that the maternal environment plays a role in inducing that error, this discovery does raise the possibility that the effect of maternal age may be somewhat less than had been assumed.

Recent studies of the safety of amniocentesis also provide an opportunity to reconsider the benefits and risks of the procedure in relation to the risks of bearing an affected child. Reliance on strict benefit-risk analysis in genetic screening is problematic because many important benefits are intangible and subjective. Whether the benefits outweigh the risks, therefore, is largely a matter of personal values; not only must

<sup>53</sup> R.E. Magenis *et al.*, *Parental Origin of the Extra Chromosome in Down's Syndrome*, 37 *HUM. GENETICS* 7 (1977).

the mathematical probability of two events be compared but also a personal valuation of their relative severity must be made. A woman who desperately wants to continue her pregnancy (perhaps her first after many years of trying) may regard the risk of the procedure as higher than the risk of bearing a Down Syndrome child. In contrast, another woman (perhaps one who is already a mother) may strongly wish to avoid the risk of a Down Syndrome child, even when achieving that perceived benefit requires a diagnostic procedure with its own risks.

Subjective assessments of risk are particularly important when the mathematical probability of two events occurring is similar. For example, the probability of the most serious harm—fetal loss from amniocentesis—appears to be .5% or lower, while the probability of bearing an affected child ranges from about .13% at age 32 to .56% at age 38. The likelihood of losing a fetus is thus generally proportionate to the likelihood of bearing an affected child in this age range; in contrast, for very young mothers the likelihood of bearing an affected child is considerably less than that of harm through amniocentesis.

Finally, current policies regarding amniocentesis for “advanced age” mothers must be examined in relation to the availability and elasticity of resources. Amniocentesis is frequently termed a “scarce resource,” and the need to ration its use justified on that basis. However, restricting demand for a service because the facilities and trained personnel to provide it are perceived to be limited can inhibit the possible expansion of the service, which would in turn accommodate a larger demand.<sup>54</sup> (This is particularly true with respect to the for-profit laboratories, but it also applies to state-operated facilities that have to compete for funds in legislative and bureaucratic arenas.) When amniocentesis first became available, the buildup of facilities was expected to be slow—perhaps slower than the buildup of demand. Although the number of amniocenteses performed has increased steadily in the past several years, only a small proportion of the potential candidates are using the service. This has been attributed to a lag in introducing the technology into clinical settings (including a failure of physicians to refer patients for the test), rather than refusal of the technique by informed women.<sup>55</sup> Moreover,

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<sup>54</sup> See National Institute of Child Health and Human Development, ANTENATAL DIAGNOSIS: REPORT OF A CONSENSUS DEVELOPMENT CONFERENCE, Dept. of Health, Education and Welfare, Washington (1979) at I-151-56.

<sup>55</sup> David C. Sokal *et al.*, *Prenatal Chromosomal Diagnosis: Racial and Geographic Variation for Older Women in Georgia*, 244 J.A.M.A. 1355 (1980); Abby Lippman-Hand and David I. Cohen, *Influence of Obstetricians' Attitudes on their Use of Prenatal Diagnosis for the Detection of Down's Syndrome*, 122 CANADIAN MED. J. 1381 (1980).

women who obtain amniocentesis are disproportionately white and urban.<sup>56</sup>

This review of the "35-and-over" policy for amniocentesis leads to two conclusions, one general and the other specific. **First, as limitations on access move from the research context to implicit (or explicit) policies on the availability of a genetic service they should be subjected to review by a broadly based process that will be responsive to the full range of relevant considerations, to changes in the facts over time, and to the needs of the excluded group(s). Second, in light of the facts concerning this particular policy the Commission believes that the common medical practice of only informing women age 35 or older about amniocentesis should be reevaluated to determine whether fairness and equity would support a more flexible policy that made amniocentesis more generally available to younger women.** This need for a reconsideration of the age criteria for amniocentesis has been recognized by the AMA Council on Scientific Affairs and others.<sup>57</sup>

One concern is that sudden less restricted access to amniocentesis might have the effect of overwhelming the existing capacity for performing the procedure, with the result that some of the women who have the greatest need would fail to receive the test while those at lower risk do have it. Thus **it is important that the elasticity of the capacity for amniocentesis is studied. A policy of increasing access for younger women should not interfere with the goal of making the test more available to women at highest risk who want to have access to it.** Moreover, amniocentesis is a costly procedure: it may not be efficient or equitable in light of other demands on scarce resources to expend public funds for groups at low risk, although this should not preclude individuals from paying for the procedure with private funds.

**Distributing Risks.** Inherent in the allocation of benefits is an allocation of their reciprocal risks (that is, the burdens that may befall people who do not receive the benefits). Sometimes, however, the distribution of risks is more apparent, as, for example, in decisions about the standards for genetic screening.

The appropriate requirement for a particular test depends on the objective of the screen. Screening tests that try to identify a high-risk population for subsequent preciser diagnos-

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<sup>56</sup> Melissa M. Adams *et al.*, *Utilization of Prenatal Genetic Diagnosis in Women 35 Years of Age and Older in the United States*, 139 AM. J. OBSTET. GYNECOL. 673 (1981).

<sup>57</sup> Council on Scientific Affairs, *Council Report: Genetic Counseling and Prevention of Birth Defects*, 248 J.A.M.A. 221 (1982); Lewis B. Holmes, *Genetic Counseling for the Older Pregnant Woman: New Data and Questions*, 298 NEW ENG. J. MED. 1419 (1978).

tic testing need not achieve as high a degree of accuracy as must a test that is not followed by confirmatory studies. PKU screening is an example of the former type of test; some prenatal diagnostic procedures illustrate the latter category. Errors in any test could lead to unnecessary anxiety or unfounded reassurance, from either of which could follow consequences contrary to the intent and expectations of the families and physicians involved. But the danger is plainly much greater when no further diagnostic steps are usually employed.

Of special concern in evaluating a test's accuracy are its sensitivity and specificity. Sensitivity is a measure of the proportion of people with the disease who test positive, while a test's specificity is the proportion of those without the disease who test negative. The sensitivity and specificity of a test are inversely related. For example, increasing a test's sensitivity to pick up more cases decreases the specificity by labeling more unaffected people as affected. Striking a balance between sensitivity and specificity is not solely a technical matter. It requires value preferences to guide the distribution of the risks, as well as evaluation of the health care system's capacity to respond to the consequences of the policy chosen. The benefits and burdens of false positive and false negative findings for a particular test must be weighed and the sensitivity and specificity set so as to do the least harm and distribute the benefits and burdens most equitably. This amounts to an intersection of ethics and public policy since it requires an application of the principle of justice.

False positive results lead to needless anxiety and corrective steps, and—where the risk of such false results is recognized—also the cost, inconvenience, and possible danger of undergoing additional tests. Of greatest concern are the cases in which mistaken diagnoses are not identified in subsequent testing and individuals or couples may make difficult choices to forego reproduction, terminate a pregnancy, or initiate arduous and sometimes harmful treatment regimens unnecessarily.

False negatives can also be harmful. The false reassurance they provide fails to prepare those involved medically, emotionally, or psychologically for a pregnancy outcome or manifestation of disease. False negative results are actually more harmful than having no test. In the latter case, a person who understands the probability of a genetic disease may take appropriate steps (for example, a couple at risk for an autosomal recessive disorder might decide not to conceive a child), while a false negative result effectively discourages recognition that the risk of the disease is a reality (as in newborn screening, when a false negative may mean that an infant who could have been spared the harmful effects of a



genetic disease, if it had been identified and the child had started on an appropriate regimen early, is instead not treated and suffers premature death, mental retardation, or other severe consequences). Whereas false positive diagnoses can be corrected in subsequent tests, a false negative generally eliminates the individual from the screening protocol with the result that the error may not be recognized until it is too late for effective corrective action to be taken.

Frequently this weighing of benefits and harms leads public health officials to make a test "oversensitive." The intent is to have no false negatives even though a large number of false positives may result. PKU screening (which has a false positive rate of over 90%) illustrates the ethical and public policy considerations underlying the design of genetic screening programs. A positive result on an initial PKU test probably causes new parents anxiety and requires an additional test in the doctor's office. But PKU tests are simple, inexpensive, essentially painless, and without risk. Thus the anxiety, the need for a follow-up visit (which may add only a small financial and logistical burden if it coincides with a routine newborn checkup), and possibly a small fee are the major consequences of an initial false positive test. If the subsequent test establishes that the disease is not present, this is the extent of the harm. In contrast, a false negative result likely dooms the child to severe mental retardation that could have been averted had the disease been diagnosed and appropriate treatment initiated. As discussed in Chapter One, the development of an effective dietary treatment has drastically reduced the number of children suffering from mental retardation due to PKU.<sup>58</sup> False negative results prevent screenees from benefiting from this important therapeutic intervention,

Program planners should also consider the predictive power of a test for a prospective screening population. This is the proportion of all positive tests that are true cases. A test that yields many false positives to produce a true positive has a low predictive power and may be too costly or burdensome to initiate. For a given sensitivity and specificity, the rarer the disease, the lower the predictive power.

The nature of the test and the capacity of the system to obtain test results efficiently are important factors in determining acceptable sensitivity, specificity, and predictive power, however. In addition to a PKU test being simple, quick, essentially without pain or risk, and cheap, it can be automated, which facilitates the processing of large numbers of samples in a short time. These considerations have made it feasible to screen the entire population and to set the cutoff level such that a large number of false positives result.

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<sup>58</sup> M. L. Williamson *et al.*, *Correlates of Intelligence Test Results in Treated Phenylketonuric Children*, 68 PEDIATRICS 2 (1981).

Furthermore, a second test is highly diagnostic, eliminating most false positives. These factors, together with the conclusion that the harms of false negatives on the initial test are more serious than those of false positives, provide the ethical grounds on which public officials initiated testing (even though the incidence of the disease and the predictive power of the test are low) and opted to make the PKU test “oversensitive” by setting the cutoff level very low.

Genetic diseases are rare. Thus in a screening program involving thousands of screenees, most of whom are normal, even a 1% false positive rate could result in a large number of misdiagnoses. Moreover, the stakes involved in genetic testing are high—decisions may be made about reproduction, and even in some cases about termination of a pregnancy, on the basis of test results. Screening ought, therefore, typically to be restricted to “high-risk” groups. This policy would also conform to goals of economy and efficiency, since the cost of a large-scale screening program can be substantial in proportion to the small number of cases detected when the population has a very low incidence of a disease.

Questions of equity and justice underlie a determination of which groups are at a high enough risk for screening and at what point the predictive value of a test is sufficiently high. Since the balance of benefits and harms from a test’s false positives and false negatives will vary with the incidence of a disease within a group, the value of screening must be determined separately for different subpopulations. The principles of equity should be reflected in the design of all genetic screening programs. **Equity is best served when a decision whether to promote screening for a particular population reflects a balancing of benefits and harms, given the incidence of the disease in the population, rather than an aim to give equal access to screening to all groups, regardless of the population-based incidence.**

**Uses and Limits of Cost-Benefit Analysis.** Cost-benefit analysis has become a recognized tool for making allocational decisions in a broad range of areas, including health care. It can help answer resource allocation and access questions concerning genetic screening and counseling, provided the significant limitations of the method are clearly understood.

Cost-benefit analysis is most useful when the costs and benefits of the action under consideration are tangible, can be measured by a common unit of measurement, and can be known with certainty. These conditions are rarely satisfied in public policy situations and they can be particularly elusive in genetic screening and counseling programs. For example, cost-benefit calculations can accurately evaluate the worth of a projected prenatal screening program if the only costs measured are the financial outlays [that is, administering a

screening and counseling program and performing abortions when defects are detected) and the benefits measured are the dollars that would have been spent on care of affected children. But the calculations become both much more complex and much less accurate if an attempt is made to quantify the psychological “costs” and “benefits” to screenees, their families, and society.

A more fundamental limitation on cost-benefit analysis is that in its simplest form it assumes that the governing moral value is to maximize the general welfare (utilitarianism). Simply aggregating gains and losses across all the individuals affected omits considerations of equity or fairness. Indeed, cost-benefit methodology itself does not distinguish as to *whose* costs and benefits are to be considered. But in the case at hand, it is an ethical question as to whether the costs and benefits to the fetus are to be considered, and, if so, whether they are to be given the same weight as those of the mother and family.

It is possible, however, to incorporate considerations of equity or fairness and thereby depart from a strictly utilitarian form of cost-benefit analysis either by weighting some costs or benefits or by restricting the class of individuals who will be included in the calculation. In any case, **cost-benefit analysis must be regarded as a technical instrument to be used within an ethical framework (whether utilitarian or otherwise), rather than as a method of avoiding difficult ethical judgments.**

In general, the process of attempting to ascertain the costs and benefits of a given policy according to a common standard of measurement performs the useful function of forcing policy-makers to envision as clearly as possible the consequences of a decision. For example, the health authorities in cities with few marriages between Ashkenazi Jews might decide not to mount a Tay-Sachs screening program, on the ground that the rarity of the expected occurrence would raise the cost-per-case-detected to a very high level in light of the expected savings. Yet their ethical analysis will need to recognize that the risk of a Tay-Sachs birth for an individual Ashkenazi couple is the same whether the benefits and burdens are distributed fairly or not.

More particularly, cost-benefit analysis can rule out some policy proposals, once ethical priorities have been fixed. It is now generally agreed, for example, that cost-benefit analysis of sickle-cell carrier screening of elementary school children would show that the benefits of the knowledge gained through screening do not outweigh the administration costs combined with the social stigma and psychological distress suffered by the screenees and their families.

The experience with sickle-cell testing and other genetic programs, together with the ethical principles discussed in this

chapter, should provide policymakers with the basis for careful preparation for tests that could become available soon.

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# Cystic Fibrosis Screening: A Case Study

# 3

The general principles set forth in the previous chapter will be matters of importance in any efforts to develop programs of genetic screening and counseling. There is some urgency that they receive thoughtful attention now because by the end of the 1980s the means are likely to be at hand for a new program of mass genetic screening of vast proportions. The disease in question—cystic fibrosis—is the most prevalent known autosomal recessive cause of serious illness and early death among Americans.

Despite intensive research, no definitive way to detect cystic fibrosis (CF) carriers or affected fetuses has been developed as yet. However, methods suitable for large-scale screening are predicted; once available, they are likely to generate great interest. Consequently, this chapter focuses on potential CF screening and counseling programs, both as a way of applying the principles developed previously and as a reminder to all concerned—physicians, genetic counselors, legislators, health agency officials, and the general public—of the great importance of thinking in advance about programs for this particular genetic condition.

## Description of the Disease

Cystic fibrosis is the most common lethal genetic disease among young people in the United States, affecting about 20,000-30,000 people.<sup>1</sup> Approximately one out of every 1800 infants is born with CF; by comparison, only about one out of every 14,000 babies in the United States is born with PKU, for which newborn screening is routine (*see* Table 1, p. 13). The

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<sup>1</sup> National Institutes of Health, *1982-1983 Research Highlights*, Bethesda, Md., mimeo. (1982) at 2.

incidence of CF in American blacks is about one-tenth the incidence in Caucasians, and the disease is almost never seen in Orientals or African blacks.

Advances in managing symptoms have increased the life span of people with cystic fibrosis in the 50 years since it was first identified as a distinct disease. Despite this progress, most CF victims today do not survive past their teenage years. Although the improvements in treatment have been palliative and both the causative biochemical defect and the cure for CF remain a mystery, research holds promise for significant advances in treatment and care.

CF is characterized by pulmonary and digestive malfunction and by abnormally high concentrations of electrolytes in a person's sweat. The pancreatic insufficiency, the pulmonary problems, and most of the other clinical manifestations of the disease are largely secondary to CF's main characteristic—a dysfunction of the exocrine (secreting) glands that leads to abnormal amounts of mucus that can obstruct organ passages. Within the first few months of life CF can be diagnosed through a "sweat test" that detects high electrolyte concentrations. In fact, the old wives' tale that a baby whose brow tastes salty when kissed will not live long probably arose from observations of infants who had CF.

CF is inherited in an autosomal recessive pattern. About one in 20 whites and one in 60 blacks in the United States is heterozygous for the CF gene; these carriers do not manifest any identifiable symptoms of the disease. (With random mating, about one white couple in every 400 and one black couple in every 3600 would be a carrier-carrier pairing, and each child they had would face one-in-four odds of having CF.) By comparison, about one Ashkenazi Jew in 30 is a carrier for Tay-Sachs disease and about one black in 12 carries the gene for sickle-cell anemia, the next most common lethal genetic disease in the United States. Due to the proportion of the US population that is Caucasian, the frequency of CF carriers in the entire population is five times that of sickle-cell carriers.

CF affects a vastly larger population than the other genetic diseases for which mass screening programs have been undertaken: essentially the entire U.S. population [at least those with some Caucasian lineage) is "at risk." No "high-risk" subgroup, except individuals with a family history of CF, has been identified. The development of screening tests for CF could, therefore, trigger the largest demand for genetic screening and counseling ever experienced in this country.

### **Development of a CF Screening Test**

**Continuing Research Efforts.** Current efforts to develop newborn, carrier, and prenatal tests for cystic fibrosis started 20 years ago with a search for a CF "factor." Because of the

generalized exocrine gland dysfunction in CF, scientists postulated that some factor, produced as an abnormal gene product and circulating throughout the body, underlies the pathology of the disease. This theory gained further credence in 1967 when investigators first reported that serum from CF patients and from obligate heterozygotes (that is, the parents of someone with CF) caused a disruption in the beat of cilia (the minute, whip-like projections from the cell wall) in rabbit trachea.<sup>2</sup> Since then, many factors have been postulated and studied. Unfortunately, none have been found to be unequivocal "markers" for CF.

**Newborn screening.** A test that measures levels of trypsin (an enzyme secreted by the pancreas) in the blood is now being studied in a statewide newborn screening program in Colorado; studies of this and related techniques are also under way in New Zealand, the United Kingdom, and several West European countries. In Colorado, the parents of all newborns are being asked to permit investigators to use part of the dried blood sample obtained for PKU testing to study the trypsin screening method. The two-year study began in April 1982 and by November over 40,000 newborns had been tested. Infants with a positive test are given a sweat test to confirm the diagnosis. Results thus far have been promising.<sup>3</sup>

**Carrier tests.** Research on carrier testing is being actively pursued by a number of laboratories in the United States, Europe, and Australia. The approaches include complex biochemical assays of biological fluids and/or cellular materials (particularly skin fibroblasts), attempts to produce an antiserum and monoclonal antibodies to some circulating immunological factor, and most recently the use of molecular biology to develop a "marker" to be used in carrier testing and prenatal diagnosis.<sup>4</sup>

Attempts to develop a carrier test have been characterized by a combination of high promise and sad disappointments. In

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<sup>2</sup> J.A. Mangos, N.R. McSherry, and P.J. Benke, *A Sodium Transport Inhibitory Factor in the Saliva of Patients with Cystic Fibrosis of the Pancreas*, 1 PEDIATRIC RESEARCH 436 (1967).

<sup>3</sup> As of November 1982, 11 newborns had tested positive on the initial screening and on the repeat test. CF has been confirmed by a sweat test in 7 of the 11 cases. In addition, CF has been diagnosed in two infants who tested positive the first time but who did not receive a repeat test. Repeat tests on another 13 newborns who tested positive initially were still being completed at the end of 1982. No cases of false negatives have been identified in the course of this study. Information provided by personal communication with Dr. Keith Hammond, University of Colorado (1983).

<sup>4</sup> See generally, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *SPLICING LIFE*, U.S. Government Printing Office, Washington (1982) at 38-41.

January 1981, for example, the news media heralded the results of a new scientific report; it appeared that the cellular response of skin fibroblasts to the drug ouabain offered a way to detect CF carriers.<sup>5</sup> In continued retesting, however, the results proved unreliable, and in July 1981 the researchers announced that the method did not work.<sup>6</sup> Other approaches have shown similar promise, only to be followed by unacceptable results in subsequent blind sample testing or when undertaken by another research laboratory.

**Prenatal diagnosis.** The search for a test for prenatal diagnosis of CF has encountered similar letdowns. For example, one method was based on the decreased activity of a proteolytic enzyme in people who have the disease. Second-trimester amniotic fluid samples from a number of at-risk pregnancies were tested for this enzyme. In the first 69 monitored pregnancies that resulted in full-term live births, however, comparison of actual outcome with the predicted outcome indicated an unacceptably high rate of both false positives and false negatives. Indeed, the overall results were not statistically better than chance.<sup>7</sup> The basis and validity of this method has been called into question.<sup>8</sup>

Other methods of detecting CF prenatally look encouraging, although false positive and false negative rates remain too high.<sup>9</sup> Rapid advances in fields such as biochemistry, cell biology, and molecular biology (particularly employing recombinant DNA technology) are being incorporated into research protocols. Following an April 1982 conference the Cystic Fibrosis Foundation was optimistic that the collaborative efforts of researchers, aided by the cooperation of the CF clinical community in providing samples for study, will ultimately result in reliable CF screening methods.<sup>10</sup> Of course, it is not possible to predict how soon such tests will be available.

As research into CF tests proceeds, experts are establishing the scientific criteria an acceptable test must meet. For example, screening will need to differentiate possible hetero-

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<sup>5</sup> *Cystic Fibrosis Study Sees Promise in Test to Identify Disease Carriers*, N.Y. TIMES, Jan. 1, 1981, at 1.

<sup>6</sup> J.L. Breslow, Joseph McPherson, and B.S. Joseph, *Sodium Transport in Cystic Fibrosis Fibroblasts Not Different from Normal*, 304 NEW ENG. J. MED. 1 (1981).

<sup>7</sup> *Heterozygote Detection and Prenatal Diagnosis: Conference Report*, New York, March 30-April 2, 1982, Cystic Fibrosis Foundation, Rockville, Md., mimeo. (n.d.).

<sup>8</sup> B.R. Branchini *et al.*, *4-Methylumbelliferylguanidinobenzoate Reactive Plasma "Protease" in Cystic Fibrosis in Albumin*, 1 LANCET 619 (1982).

<sup>9</sup> Henry L. Nadler, Phyllis Rimbelski, and Kathi Hanna Mesirov, *Prenatal Detection of Cystic Fibrosis*, 2 LANCET 1226 (1981).

<sup>10</sup> *Heterozygote Detection and Prenatal Diagnosis: Conference Report*, *supra* note 7, at i.



geneity in the genetic defect responsible for CF. As described in Chapter One, an incomplete understanding of the heterogeneity of the genetic defect that causes hyperphenylalaninemia led to confusion and misleading test results in the early stages of PKU screening. In addition, the enormity of the potential demand for CF screening makes it important that the tests that are developed can be automated.

**Ethical Issues During Research.** As with all research, studies of prospective CF tests require careful attention to ethical issues. Investigators must comply with specific procedures intended to protect human subjects, including prior review and approval of the study by an Institutional Review Board.<sup>11</sup> Issues of concern in CF screening include the selection of subjects, the disclosure of results to participants, and the monitoring, oversight, and funding of adequate pilot studies.

**Subject selection and disclosure of results.** Blood samples for experimental newborn screening can be readily obtained in large numbers by obtaining proper consent for the use of samples already collected from most newborns during PKU screening. In contrast, investigating a CF prenatal test requires recruiting women to have amniocenteses they would not otherwise undergo.<sup>12</sup> In the early stages of such research, fluid samples from women who have had amniocentesis because of their increased risk for other biochemical or chromosomal defects are useful. However, this group is not representative of the potential target population for CF prenatal screening. Ultimately, research on women known to carry the CF gene (that is, women who have already borne a child with CF) is required.

When research subjects risk injury—and amniocentesis carries a small risk—it is preferable that those who bear the burdens of research also benefit from it to the greatest possible extent. As a group, those with an increased risk for bearing children with CF stand to gain the most from development of a screening test. Indeed, the eagerness to advance research in this area is one incentive for women to participate in the research; the provision of a cytogenetic analysis of the amniotic fluid, including identification of the sex of the fetus, at no cost to the subjects could be another benefit. However, the most desirable benefit for subjects is information about whether they are carrying a child with CF. Yet reporting the results of experimental CF tests to the subjects could have scientific as well as ethical ramifications.

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<sup>11</sup> 45 CFR 46.

<sup>12</sup> A small number of women at increased risk for CF may be candidates for amniocentesis because of “advanced maternal age” or other reasons. However, the overlap is not likely to be sufficient to avoid some women having to undergo amniocentesis solely for research purposes.

CF cannot be definitively diagnosed in an aborted fetus: prenatal test results can be verified only by performing a sweat test on an infant after birth. Establishing the sensitivity and specificity of a prenatal test depends, therefore, on subjects continuing their pregnancies to term. If a significant portion of the participants in a CF prenatal study were to terminate their pregnancies, research goals could not be met—and thus all the women who participated in order to advance research would have undergone amniocentesis pointlessly.

The importance of refraining from actions based on unproven test results is not solely a matter of scientific concern, however. If the accuracy of test results is unknown, then actions based upon them may cause rather than prevent harm. The harm that could result from false positive results varies with the type of test. Parents who are told that their newborn may have CF are likely to suffer considerable anxiety until a sweat test can be done; this test may also be associated with minor inconvenience or expense. In contrast, a “positive” result in a prenatal study might lead a couple to terminate a pregnancy.

In light of the tentative nature of the results and the need to continue pregnancies to evaluate the test, one approach would be to withhold test results. The strongest case for withholding data is when researchers lack evidence of the test’s accuracy. As research results begin to approach a level that is scientifically valid, however, the question of disclosure of test results becomes more difficult, and turns in part on the level of proof demanded of the test. Researchers may believe that a test should have a very low false positive rate before it forms the basis for clinical decisions. On the other hand, the parents participating in the research, many of whom have had a child with CF and are eager to have an unaffected baby, may be willing to act upon much less conclusive data; some would prefer to abort what may be a normal pregnancy rather than risk bearing a child with CF. Despite specific warnings that results are for research purposes and not for clinical decisions, some women may nonetheless make decisions about their pregnancies on the basis of preliminary CF test results.

Clearly, the degree of certainty required for scientific conclusions can differ from that considered sufficient for personal decisionmaking. Once evidence of some increase in the ability of the test to detect CF accumulates, withholding test results precludes subjects from exercising personal value judgments. Therefore, subjects should be informed in advance of participation whether results will or will not be disclosed. If results are reported, their limitations should be fully explained to the subjects.

***Assuring adequate pilot studies.*** If limited trials of possible CF screening tests are successful, larger-scale pilot

studies will be needed; their scope will depend on the numbers required to obtain statistically valid data. In addition to ascertaining how well a test works from a scientific or statistical perspective, pilot studies should also evaluate other aspects of the screen, such as cost-effectiveness, measures to educate professionals and the public about the test, and laboratory performance.

The promising research into CF screening tests that is under way gives particular urgency to the Commission's recommendation that researchers, along with government, industry, and other funding and regulatory sources, begin now to identify their respective roles in adequate premarket testing of new screening methods.

### **Planning Programs for Carrier and Prenatal Testing**

If a carrier and/or prenatal test proves acceptable in pilot studies, planners will need to identify who to screen and in what setting. Both the likely benefits and harms to potential screenees and the relative costs and benefits to society will need to be evaluated. Outside a research setting, screening programs ought to be introduced only if they seem likely to offer a net benefit to those being screened. The benefits of carrier and prenatal tests differ and will be influenced by the order in which the tests become available. Clearly, families who have a child with CF view the tests differently from those who do not.

**Assessing Potential Benefit and Harm.** Prenatal diagnosis for CF is likely to be developed either in conjunction with the discovery of a carrier test or in advance of it, depending upon the method that first proves successful [for example, biochemical or recombinant DNA]. The availability of a prenatal test would eliminate some of the difficulties that arise when only carrier testing is available; in the latter case, test results may be used to select mates or to decide whether to forego childbearing but not to determine the outcome of a particular pregnancy. The contrasting experiences of screening for sickle-cell anemia (before the recent development of a means of prenatal diagnosis) and Tay-Sachs disease are illustrative. Some potential sickle-cell screenees found that the availability of carrier screening without prenatal diagnosis was more harmful than helpful since they did not wish to make decisions based on carrier status alone. With Tay-Sachs disease, the simultaneous availability of a carrier test and prenatal diagnosis (and selective abortion) led some carrier couples to try to have children rather than forego reproduction entirely.

Although the experiences with sickle-cell and Tay-Sachs screening are instructive, neither is perfectly analogous to CF testing.<sup>13</sup> Like sickle-cell anemia, CF can be variable and is susceptible to some palliative treatment; although not as rapidly lethal as Tay-Sachs, CF is usually a very burdensome condition. Moreover, there are sociocultural as well as individual differences in the assessment of the benefits of prenatal diagnosis based on the importance people attach to health and to medicine generally and on their attitudes toward abortion.

In this way, the potential for CF screening is a precursor of the many difficult issues of risk and benefit that will increasingly arise in various types of genetic testing. The expanding capability to detect conditions and even predilections toward diseases prenatally—including, perhaps, some that occur later in life—underscores the importance of individuals freely choosing whether to participate in screening.

**Deciding Who and When to Screen.** Careful consideration will need to be given to the relative advantages and disadvantages of the two possible approaches to CF screening: prospective and retrospective testing. A prospective program would extend to the general population or some segment of it (for example, couples considering childbearing). It would require extensive educational efforts to provide information about CF to people who are unacquainted with the disease. A retrospective program would be limited to families that include someone with CF. These candidates would already have some familiarity with the condition.

There are several ways that prospective screening could be organized. It could be provided in a community-based or mass screening program in which community resources are used to inform people about the disease and the test and in which screening is made widely available. Some experts have questioned this approach for diseases with a low incidence, however, arguing that the anxiety and stigmatization that can result from such a mass screening effort can outweigh the benefits when the likelihood that an individual screenee will produce an affected child is small.<sup>14</sup> This question will need to be addressed in the planning of a CF program, especially in

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<sup>13</sup> One reason for the greater acceptance of Tay-Sachs screening is the seriousness of the disorder itself; after a few months of normal development, affected infants begin to undergo a tragic degeneration, followed by death at a very young age. In contrast, the clinical effects of sickle-cell anemia vary considerably; patients can reach adulthood with symptoms ranging from quite mild to very severe.

<sup>14</sup> Madeleine J. Goodman and Lenn E. Goodman, *The Overselling of Genetic Anxiety*, 12 HASTINGS CTR. REP. 20 (Oct. 1982); Arno G. Motulsky, *Brave New World? Current Approaches to Prevention, Treatment and Research of Genetic Diseases Raise Ethical Issues*, 185 SCIENCE 653 (1974).

deciding whether to screen populations with a very low incidence of the disease. CF is very rare in American blacks, for example. Just as individuals without eastern Jewish heritage are not screened for Tay-Sachs disease and Caucasians are not screened for sickle-cell anemia, CF screening of American blacks is probably inappropriate. In the past, screening for PKU was discontinued in predominantly black cities (such as Washington, D.C.) because PKU is so rare in blacks that the costs of screening were seen to outweigh the benefits.

In defining the target population a decision will also have to be made about whether to offer screening to people who are unmarried or not of reproductive age. The US. experience with sickle-cell screening of schoolchildren—about whom confidentiality was often difficult to maintain—sounds a warning about screening a population in which the benefits are so remote that they are likely to be outweighed by the harm, including the risk of breach of confidence. The young children screened for sickle-cell could do nothing with the information, and serious problems of stigmatization and confusion over the meaning of carrier status injured those screened and gave the whole effort a bad name.<sup>15</sup>

Alternatively, it is at least theoretically possible to obtain nearly as complete an identification of at-risk cases through screening solely married couples and people planning marriage as through general screening.<sup>16</sup> Initially, most Tay-Sachs screening involved only married couples because the programs' organizers (which typically included rabbis and other leaders in the Jewish community) did not want to risk having carrier status influence marital choices (and saw no need for such an influence, since amniocentesis was available for carrier-carrier couples). This policy reflected an understandable sensitivity to the risk that the label "carrier" might stigmatize a person in the eyes of others (including prospective mates and their families) as well as lead to a loss of self-esteem. Since children would not need the information to make reproductive decisions, there was no reason to risk the stigma.<sup>17</sup>

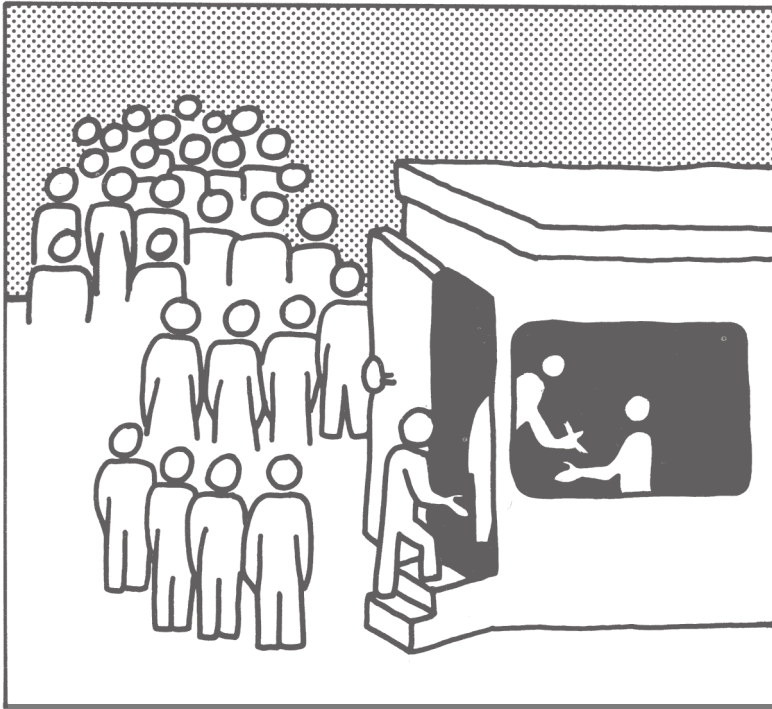
Although concerns over the possible harm of stigmatization are important, they must be weighed against the value of

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<sup>15</sup> Ernest Beutler *et al.*, *Hazards of Indiscriminate Screening for Sickness* (Letter), 285 NEW ENG. J. MED. 1485 (1971).

<sup>16</sup> Arno G. Motulsky, George R. Fraser, and Joseph Felsenstein, *Public Health and Long-Term Genetic Implications of Intrauterine Diagnosis and Selective Abortion*, 7 BIRTH DEFECTS: ORIGINAL ARTICLE SERIES (No. 5, 1971) at 22.

<sup>17</sup> This strict policy in the early Tay-Sachs programs has been relaxed in light of demands for the test from unmarried individuals, particularly those with a Tay-Sachs victim in the family.



early screening. Many people may wish to know their carrier status prior to marriage (though not all of them may have thorough premarital medical examinations) and some do not wait until marriage to conceive children. This raises the question of whether people would generally regard it as desirable for decisions about dating, marriage, and reproduction to be made (at least in part) on genetic grounds. The outcome of the balancing process in the case of CF screening will depend upon facts about the test and the auspices and procedures for implementing it. The benefits of administrative efficiency in screening easily accessible populations (such as schoolchildren) will need to be weighed against all the harms, including nonphysical risks to individuals and society.

The alternative to a community-based program would be physician-based screening. If both prenatal and carrier tests were available, obstetricians could provide screening. All pregnant women could be offered the heterozygote test, partners of carriers could be screened, and “carrier couples” could be offered prenatal diagnosis. One drawback of this approach is that some couples or individuals, particularly those who would not want prenatal diagnosis, may wish to know whether they are carriers before marrying or conceiving a child. An obstetrics-based screening program would be inadequate in these cases. Screening offered as part of more generalized medical care (internists, gynecologists, and family

practitioners) might be more responsive to this demand, but would still exclude a large number of potential screenees who do not receive regular medical care. Physician-based screening would require improved understanding of genetic diseases among physicians who are not specialists in genetics.<sup>18</sup>

If retrospective instead of prospective screening were used (for example, if a prenatal test were developed before a cost-effective means of carrier screening), the physician-based rather than the community-based approach would have to be employed. In terms of reducing the incidence of CF, the impact of retrospective screening would be much less than large-scale prospective screening.

Under a scheme of prospective diagnosis the case reduction is 100% (i.e. no cases with the disease are born), as opposed to the less effective reduction which can be achieved with retrospective diagnosis (i.e. following birth of an affected child). Considering only the economic aspects, the saving to society by not having to bear the high costs of supporting patients with cystic fibrosis for the relatively large number of years which they can now survive will probably be substantially greater than the continuing costs of the programs for premarital screening, for intrauterine diagnosis and for selective abortion once the use of automated devices is introduced.<sup>19</sup>

As the Commission has noted throughout this Report, however, the fundamental value of genetic screening and counseling lies in its potential for providing individuals with information they consider beneficial for autonomous decision-making. Therefore, although societal impact and cost-effectiveness are relevant considerations, the benefits and harms that could accrue to individual screenees deserve special consideration if retrospective CF screening is being contemplated.

**Distributing Benefits.** The potential demand for CF screening is so large that even if a rather sizable portion of it does not materialize an enormous demand for genetic counselors and other health care personnel and services could still be engendered. Since CF tests should not be offered unless support

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<sup>18</sup> In a 1974 survey of a random sample of pediatricians, obstetricians/gynecologists, and family physicians, nearly three-quarters of the group reported that no courses in genetics had been available during their medical training. The study found that the medical profession as a whole is not ready to accept the importance of genetic disease, but that readiness could be increased if physicians had greater knowledge of human genetics. Committee for the Study of Inborn Errors of Metabolism, GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH, National Academy of Sciences, Washington (1975) at 161-64.

<sup>19</sup> Motulsky, Fraser, and Felsenstein, *supra* note 16, at 24.

services are adequate, program objectives must either provide for the expansion of needed resources, especially trained personnel, or limit screening initially in a manner that would distribute it equitably.

An important objective, therefore, for those with responsibility for genetic screening programs will be to guarantee that needed resources, or the means of generating them in an orderly fashion, are available as screening is offered. Because the National Genetic Diseases Act was replaced by the Omnibus Reconciliation Act of 1981, greater responsibility for adequate preparation now rests with the states (from funds provided in block grants for maternal and child health programs) and with voluntary and professional organizations.<sup>20</sup> The states that had the strongest and best developed programs before 1981 may have the best chance of receiving non-Federal funds because successful programs typically develop local supporters who help lobby for grants. Conversely, where there has been little effort to date, the medical and lay communities may be unable to articulate the need for programs convincingly, even though the unmet need in such localities may actually be greater than elsewhere and the ability of preliminary programs to generate funds from other sources is usually less. Private organizations and government agencies should therefore pay particular attention to developing services in those areas.

Without knowing the type of test that might first become available, it is impossible to predict precise resource demands. A multiphasic test that uses several technologies (as in tests for neural tube defects done with blood samples after AFP testing, for example) would require different resources than a single biological assay. Nevertheless, it should be possible to begin to analyze the impact that large-scale CF screening, as well as other forms of genetics services, could have on the health care system.

A rough approximation of the number of tests an obstetrics-based system would involve can be calculated as follows: screening 3.3 million pregnant women (the approximate number of live births each year<sup>21</sup>) would yield about 165,000 carriers (assuming a carrier frequency of 5%); if the partner of each carrier is then screened, about 8250 couples who are carriers would be identified. Theoretically, therefore, the

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<sup>20</sup> The voluntary groups include disease-based foundations, such as the Cystic Fibrosis Foundation, and umbrella groups, such as the National Foundation-March of Dimes. The American Society of Human Genetics provides leadership in professional activities relating to medical genetics.

<sup>21</sup> As this figure does not include miscarriages, the total number of women screened could be even higher, depending on when the miscarriages occurred in relation to the timing of a prenatal test.



capability to perform more than 3.4 million carrier tests and 8250 prenatal tests annually would be needed even under the narrowest form of prospective screening (that is, obstetrics-based). Of course, not all women obtain medical care early enough in pregnancy for prenatal diagnosis, and some pregnant women or their partners may choose not to undergo the carrier or prenatal test, so that demand will not be fully realized. Still, trying to meet even part of that demand would put a considerable strain on the health care system.

Alternatively, a mass screening program to detect carriers that was targeted, for example, at Caucasians of reproductive age could create a demand for many millions of tests in a short period of time. Large numbers of trained counselors and other public health personnel would be required, in addition to widespread public education and community involvement.

**Involving and Educating the Public.** The generalized nature of the population at risk for cystic fibrosis in the United States has implications for the types of public education programs and local involvement in screening that will be suitable for this disease. A mass screening program will not be able to rely on any preexisting subgroups in the population affected who have special interest in the tests, as has been done with other genetic diseases. Planners would need to turn to a larger and more diverse range of organizations and individuals, both locally and nationally, to achieve public participation. They will have to be very resourceful in identifying how members of the public can become informed about the availability and objectives of the screening and participate in planning local programs.

Although it may seem obvious that realistic goals for the program should be understood by the public, difficulties have arisen in the past when this has not occurred. Enthusiasm for mandatory PKU screening legislation, for example, was propelled in part by misguided notions that the test would significantly reduce the burden on public institutions for the mentally retarded when in fact less than 1% of the institutionalized retarded had PKU.<sup>22</sup>

## Planning a Newborn Screening Program

**Assessing Benefits and Harms.** The value of the most widely used neonatal genetic test—for PKU—is that early diagnosis and treatment averts serious disease complications. For cystic fibrosis, however, it is not clear that a diagnosis in the neonatal period would usually affect outcome or even alter therapy. CF is not always recognized at the first sign of

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<sup>22</sup> GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH, *supra* note 18, at 24.

symptoms but some delay in arriving at a correct diagnosis has not been thought to affect the outcome of treatment adversely.

Families with a child who has CF should already be aware of the possibility of a subsequent CF birth, and therefore newborn screening would primarily benefit those who are not aware they are carriers. The possible benefits of mass newborn CF screening (if an effective method is developed) are that it could eliminate some of the costs, frustration, parental anxiety, and harm of incorrect diagnoses and therapies. Physicians are now studying the possibility that the prognosis for CF patients improves if treatment is begun before the onset of clinical signs. In addition, prospective newborn screening would provide the parents of a CF child with an earlier warning that they are CF carriers and, therefore, that any other children they conceive have a 25% chance of having cystic fibrosis. On the other hand, presymptomatic identification of CF may generate needless psychosocial problems within families since infants who would otherwise still be regarded as "normal" would instead be seen as sick and at risk for developing CF symptoms at any moment.

**Distributing Benefits.** In newborn screening, concerns about equity and access to services will probably be most acute in relation to follow-up tests. If the screening protocol relied on sweat testing as a confirmatory diagnostic measure, then present limitations in the reliability of such tests not done in specialized centers will be a serious concern.<sup>23</sup> In deciding whether and how to implement widespread newborn screening, the feasibility of upgrading test performance in areas now inadequately served must be considered, either through specialized laboratories or through providing equitable access for patients from these areas to centers that perform the diagnostic tests reliably.

**Protecting Autonomy.** A basic ethical consideration underlying any CF screening program should be the protection of individual autonomy. Although considerable public interest has been shown in the development of a test, some individuals are likely to choose not to be screened for CF, and their ability to make that choice must be safeguarded.

The need to assure the option of refusing a CF newborn test underscores the importance of informed consent in newborn screening generally. Although most states' mandatory genetic screening statutes provide that parents may object to screening (in some cases, specifically on religious grounds),

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<sup>23</sup> *Problems in Sweat Testing*, Report of a Conference, Hilton Head, S.C., Feb. 6-7, 1975, Cystic Fibrosis Foundation, Rockville, Md., mimeo. (n.d.).

these provisions are usually ineffective since parents seldom learn about the test until after it has been performed.<sup>24</sup> Some people have concluded that “informed consent” ought not to be necessary for a procedure that offers great benefit and little risk.<sup>25</sup> According to this argument, parental autonomy in decisionmaking about newborn screening is grounded in a principle of beneficence, which holds that parents are the people most well suited to act in the best interests of an infant. When, the argument goes, it would be generally agreed that children’s best interests lie in being screened, parental consent is superfluous. But even if this case could be made for certain established screening programs—and the Commission is not wholly persuaded that it could—it certainly does not apply to a condition like CF, in which the benefits of the screening test are not clear-cut and in which parents, therefore, may choose not to participate.

Moreover, informed consent is more than just a legal formality—one more piece of paper to sign. It is a process of shared decisionmaking between patients and providers.<sup>26</sup> It can play an educational role—both in telling a pediatrician something about new parents’ values and beliefs and in informing the parents about the usefulness of obtaining evaluations even for apparently “well” children, about their mutual responsibility (along with physicians and nurses) for their child’s health, and even about probability and genetics. In addition, a process of this sort, in which parents are informed and their permission is sought for CF newborn screening, is a reminder to health care professionals and legislators of the importance of informed consent more generally.

The availability of a neonatal CF test suitable for mass screening could stimulate both a more scrupulous enforcement of the current “permissible refusal” provisions of existing laws and, even more important, lead to a reevaluation of the wisdom of mandatoriness in all newborn genetic screening. As a practical matter, a CF screen is likely to be performed on the same blood sample now obtained for other newborn tests and the need to obtain informed consent for the CF test may encourage simultaneous consent for other tests. Since parents, excited about the recent birth of their child, may prefer not to contemplate the remote possibility that their infant has a serious disease, physicians should consider initiating discus-

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<sup>24</sup> Ruth Faden *et al.*, *A Survey to Evaluate Parental Consent as Public Policy for Neonatal Screening*, 72 AM. J. PUB. HEALTH 1347 (1982).

<sup>25</sup> Ruth R. Faden, Neil A. Holtzman, and A. Judith Chwalow, *Parental Rights, Child Welfare, and Public Health: The Case of PKU Screening*, 72 AM. J. PUB. HEALTH 1396 (1982).

<sup>26</sup> President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *MAKING HEALTH CARE DECISIONS*, U.S. Government Printing Office, Washington (1982).

sions about these tests prior to delivery, at which time the genetic screening programs can be placed in the context of other medical information relevant to the impending birth.

### **Adequate Evaluation**

It is particularly important that appropriate plans for evaluation be a stated objective of initial CF screening efforts. First, since testing for CF will probably involve a much larger program than any previous genetic carrier screening efforts, careful monitoring will be needed to determine whether it is reaching its objectives. The specific questions to be answered in follow-up studies will depend on whether the screening involves prenatal, carrier, and/or newborn tests. In any event, the scientific, epidemiological, and psychosocial effects of screening all deserve careful attention.

Second, screening for cystic fibrosis is likely to provide a preview of what will in the future be an increasingly important part of health care. The lessons of CF screening can augment those of previous programs—for PKU and other newborn screening for inborn metabolic errors, for trait carriers and affected fetuses of Tay-Sachs and sickle-cell anemia, and for chromosomal anomalies in the fetus.

The ethical imperative for adequate evaluation flows from the principle of beneficence—the promotion of the well-being of those who participate in genetic screening and counseling. Moreover, follow-up studies not only provide a basis for an overall evaluation of the test; they also enhance autonomy by contributing important information for the informed consent process. Appraisal of the screening once it has become more widely available will, therefore, be needed.

The Commission believes that for some screening programs evaluation is likely to be most effective if coordinated on a national basis, whether the evaluation is done by private bodies (with or without support from a Federal agency), by state agencies, or by a Federal health agency such as the Centers for Disease Control. As described in Chapter One, this model was followed by the United Kingdom in its large-scale study of AFP testing. Public and private funding should be made available for such follow-up. The important role that state health agencies can play in this field is well illustrated by the activities of the Commission on Hereditary Disorders in Maryland, which for nearly a decade has overseen and promoted the development of screening programs in that state. The legislation that established that body provides a valuable model for other states.

## Conclusion

Within the next decade screening for cystic fibrosis may be possible. This could be of great benefit. If adequate preparation for its introduction is not made, however, it could also create serious problems. The technical aspects of such preparation are not the primary concern of this Commission; they rest with the Food and Drug Administration and with the process of peer review at Federal and private funding agencies and in scientific journals.

The likelihood of a huge demand for CF screening—of carriers, of pregnant women, or of newborns—merits attention to more than merely technical issues and to more than just CF testing, however. The possible demand for millions—or tens of millions—of tests in a short period of time, and the consequent need for follow-up diagnostic studies and counseling, is daunting in itself. Moreover, it is merely the harbinger of a still greater demand: the ability to screen for genetic conditions is certain to affect not only health care but also areas as varied as environmental control and occupational and product safety, as it becomes possible to determine personal susceptibility to particular disorders or to the risk of passing them on to offspring.

In this Report the Commission has reached a number of conclusions about what might be termed “ethical preparedness” for genetic screening and counseling. It believes that the guidance set forth here, in conjunction with that provided by other groups,<sup>27</sup> establishes a solid starting point for resolving the issues—of autonomy, confidentiality, equity, knowledge, well-being, and the like—that will arise when various types of CF testing become feasible. Some of these issues concern benefits and risks to individuals, others the welfare of the entire society, and still others a combination of both. Some of the problems are concrete—such as protecting the confidentiality of screening results. Others, which are harder to address, are more abstract—such as correcting the notion that genetic measures can, or should, be used to make the outcome of each pregnancy a “normal” person, much less a “perfect” one.

The Commission recognizes that it is unlikely that all problems can be avoided—or even that they can all be anticipated at the moment. But it encourages continued atten-

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<sup>27</sup> See, e.g., GENETIC SCREENING: PROGRAMS, PRINCIPLES AND RESEARCH, *supra* note 18; M. Lappé *et al.*, *Ethical and Social Issues in Screening for Genetic Disease*, 286 NEW ENG. J. MED. 1129 (1972); Tabitha M. Powledge and John Fletcher, *Guidelines for the Ethical, Social, and Legal Issues in Prenatal Diagnosis*, 300 NEW ENG. J. MED. 168 (1979); Council on Scientific Affairs, *Council Report: Genetic Counseling and Prevention of Birth Defects*, 248 J.A.M.A. 221 (1982).

tion to this area by government officials, as well as by people knowledgeable about relevant scientific, ethical, social, and legal concerns. This call for attention is not meant to raise an alarm, merely to point to some steps that should be taken—and, in particular, some ethical concerns that need to be addressed—to ensure that the burgeoning capabilities of medical genetics achieve their great potential for good. This field holds the promise of increasing people’s options and letting them make choices informed and free of the constraints of ignorance. By educating people about their own particular inherited makeup, genetic screening and counseling—if employed with care and with attention to the issues addressed in this Report—can increase respect for the great diversity of human beings that rests in part on their genetic heritage.

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# Glossary

## A

**Alleles** - Alternative forms of a gene that occupy identical sites on homologous chromosomes and that determine alternative characters in inheritance.

**Amino acids** - The building blocks of proteins. Each protein consists of a specified sequence of amino acids.

**Amniocentesis** - A method of prenatal diagnosis that involves withdrawal of a small amount of amniotic fluid from the amniotic sac that surrounds the fetus; the fluid contains cells shed by the fetus.

**Aneuploidy** - Deviation from the normal number of chromosomes, which in humans is 46.

**Autosome** - Any of the 22 pairs of 44 nonsex chromosomes.

**Carrier** - An individual who possesses a recessive gene together with its normal allele. Although the recessive gene is not expressed, the individual can transmit the gene to progeny who would express it if another recessive gene at the same site is inherited from the other parent. The term is also used for the presymptomatic state of an individual who carries an autosomal dominant gene.

**Chromosome** - A cigar-shaped structure containing DNA, which is located in the cell nucleus. The number of chromosomes is characteristic for a given species; the normal number in humans is 46, with 22 pairs of autosomes and 2 sex chromosomes (XX or XY).

**Congenital** - Present at birth.

**Cost-benefit analysis** - An analysis that attempts to estimate all of the consequences, both adverse (costs) and advantageous (benefits) of a proposed course of action, and places a money value on those outcomes.

**Cost-effectiveness analysis** - An analysis in which a given aim may be achieved by a number of alternative policies and the costs of achieving this fixed aim are compared (*i.e.*, how to meet a particular objective at least cost; or, given a fixed budget to meet a particular objective, how best to deploy this budget).

**Cytogenetics** - The study of the structure and function of chromosomes.

**Deletion** - Loss of part of a chromosome that results in an imbalance of genetic material.

**De novo** - When a genetic disorder occurs and is clearly not inherited, it is said to have occurred *de novo*, as a new mutation.

**Deoxyribonucleic acid (DNA)** - A nucleic acid found in all living cells, which comprises the genetic material in chromosomes. Every inherited characteristic has its origin somewhere in the code of each individual's complement of DNA.

**Dominant gene** - A gene that is expressed in a single copy (or in the heterozygous state). An autosomal or x-linked dominant disease is caused by such a gene.

**Enzyme** - A functional protein that is produced by living cells and that accelerates a chemical reaction without itself undergoing a marked change in the process.

**False negative** - A negative test result for a sample obtained from an individual who *has* the condition in question.

**False positive** - A positive test result for a sample obtained from an individual who *does not* have the condition in question.

**Fertilization** - The union of male and female germ cells or gametes.

**Fetoscopy** - A procedure that permits direct visualization of the fetus and the placenta through a device that is put through a hollow needle inserted through the abdominal wall into the uterus and amniotic sac.



**Gamete** - A male or female reproductive cell (*i.e.*, the sperm or the egg) whose union is necessary, in sexual reproduction, to initiate the development of a new individual. Gametes differ from other cells in that they contain only half the usual number of chromosomes.

**Gene** - The basic unit of heredity. It is made up of DNA and located in a definite position on a particular chromosome.

**Genome** - The total genetic endowment packaged in the chromosomes. The human genome consists of 46 chromosomes.

**Genotype** - The genetic constitution of an individual, including alleles that are not expressed.

**Germ cell** - A sperm or an egg, or a formative stage of either.

**Heterozygote** - An individual possessing a variant gene and a normal gene at identical sites of homologous chromosomes. (adjective: heterozygous)

**Homozygote** - An individual possessing an identical pair of alleles, either both normal or both variant, at identical sites of homologous chromosomes. (adjective: homozygous)

**Inversion** - A reversal of the usual gene order along a segment of a chromosome.

**Meiosis** - A type of cell division that occurs only in the germ cells during the formation of gametes in sexually reproducing organisms. Two consecutive cell divisions occur but only one division of the chromosomes occurs, thus the number of chromosomes in the gametes is reduced by half.

**Mendelian** - See monogenic.

**Mitosis** - A type of cell division in which the chromosome set of the resultant cells (daughter cells) is identical to that of the parent cell. Mitosis is characteristic of somatic cells and of germ cells before the onset of meiosis.

**Monogenic** - Traits determined by one gene or a single allelic gene pair. Also called Mendelian, after Gregor Mendel (1822-84), the Austrian abbot whose breeding experiments with peas established the pattern of inheritance for characteristics determined by single genes.

**Monosomy** - The absence of one member of a chromosome pair.

**Multifactorial** - Traits determined by interaction of multiple gene pairs with environmental factors.

**Mutation** - A structural alteration in the DNA of a gene resulting in a permanent, transmissible change in the genetic makeup of an individual such that the characteristics of an offspring are different from those of his or her parents. A mutation is usually defined as a change in a single gene (point mutation), although the term is sometimes used more broadly to describe a structural chromosomal change.

**Phenotype** - The entire expressed physical, biochemical, and physiological constitution of an individual.

**Polymorphism** - A gene that occurs in a population with a frequency too great to be explained by mutation alone.

**Protein** - A sequence of amino acids. Proteins differ from one another in their amino acid sequence. They are coded for by DNA and are the functional and structural components of cells. All enzymes are proteins.

**Recessive gene** - A gene that is *not* expressed in a single copy (or in the heterozygote state). A recessive disease is caused by two copies (or homozygous state) of such a gene.

**Sex chromosome** - Chromosomes responsible for sex determination, *i.e.*, the X or the Y chromosome. Normal human males have one X and one Y (XY); normal human females have two Xs (XX).

**Somatic cell** - One of the cells composing body tissues and body organs other than a germ cell.

**Translocation** - An error occurring during chromosomal replication, whereby a chromosome or a fragment of it becomes attached to another chromosome.

**Trisomy** - The presence of a third chromosome in cells that normally contain two, as in Trisomy 21 (Down syndrome).

**X-linked** - Any gene found on the X chromosome or traits determined by such genes; sex-linked.

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# Basic Concepts

# B

## The Genetic Building Blocks

The molecular basis of inheritance in most organisms, plant and animal, is the chemical **deoxyribonucleic acid** (DNA). The molecules that make up DNA can be thought of as code letters, capable of combining into a great variety of “words.” These “words” direct two major processes, **replication** and **protein synthesis**. Replication involves the production of identical DNA sequences so that when a cell divides, each daughter cell receives a complete copy of the original cell’s genetic information. Protein synthesis involves the production of **proteins**, such as **enzymes**, each of which plays a very specific role in the structure and functioning of the organism. Through the process of evolution, each species has accumulated its own set of genetic information that both maintains the continuity of interspecies diversity and facilitates intraspecies diversity in sexually reproducing organisms. Thus, humans give birth only to other humans, although each individual has very different physical and functional characteristics.

A **gene** consists of a small segment of DNA that directs the synthesis of **amino acids**, which are the building blocks of proteins. Genes are packaged in units called **chromosomes** (which are actually visible under a light microscope during certain stages of cell division). Human beings normally have a set of 46 chromosomes, which contain all the genes. The term **genome** is used to describe this full complement of genes; each individual (with the exception of identical siblings) possesses a unique genome. The set consists of 23 pairs of chromosomes, with each pair containing one chromosome from the mother and one from the father. The 44 chromosomes in 22 of these pairs are called **autosomes**; the two chromosomes in the 23rd pair are **sex chromosomes**. In males, this is an X and a Y (XY);

in females, two X chromosomes (XX). (Very occasionally, people have different combinations of X and Y chromosomes.)

The human body is made up of **somatic cells**—the cells composing parts of the body such as tissues and organs—and **germ cells**—eggs or sperm or their precursors. The chromosomes are contained within the **nucleus** of all these cells. During the formation of eggs or sperm the number of chromosomes is halved by a process called **meiosis**. Consequently, when an egg is fertilized, its 23 chromosomes (22 autosomes and one X chromosome) join with the sperm's 23 chromosomes (22 autosomes and either an X or a Y chromosome), resulting in the full set of 46 chromosomes. The fertilized egg then undergoes cell division (termed **mitosis**), during which identical daughter cells are formed. The development of the organism occurs through a coordinated pattern involving both multiplication of cells and their differentiation into distinct parts of the body—bones, connective tissue, muscles, and so forth. Though all the cells in a developing organism normally contain identical genes, the genetic information is expressed differently from cell to cell early in gestation. Through the process of differentiation, most of the genes in each cell “switch off,” that is, they stop synthesizing proteins. The specific proteins made by the small fraction of genes that remain active determine how the cell becomes differentiated—that is, how it functions in a limited capacity, as a blood cell or a brain cell or a kidney cell and so forth. The specialized gene products of each of these cells—the proteins—are the materials that form the structure of the organism and through which its functioning is coordinated.

### **Patterns of Inheritance**

The genetic information in the nucleus of each cell interacts with the environment in which an organism lives. Factors in the environment thus affect the way genes are expressed. Many medical geneticists study the relative significance of the genetic and environmental components of a disease or disorder. Studies of twins, of families, and of the general population have helped provide a better understanding of the contributing factors in each particular case. As a result, many diseases have been classified as “genetic” according to specific inheritance patterns that enable an expert to estimate the risk of getting the disease.

The genes are arranged in very specific patterns along the chromosomes. A change in the number, arrangement, or molecular sequence of the genes as a result of gene-gene and/or gene-environment interactions is called a **mutation**. Mutations may either occur **de novo** or be inherited. They are the basis of natural evolution. Some mutations, however, have bad consequences for the organism—these are commonly

labeled “genetic diseases.” Every human being inherits about six or seven deleterious mutations that under certain circumstances can cause serious illness.

Genetic diseases or defects can often be categorized as **monogenic** (involving a mutation in a single gene), **multifactorial** (involving an interaction between the environment and more than one gene), or **chromosomal** (caused by an imbalance in genetic material). If a disease or birth defect falls into any of these categories, risk estimates can often be calculated.

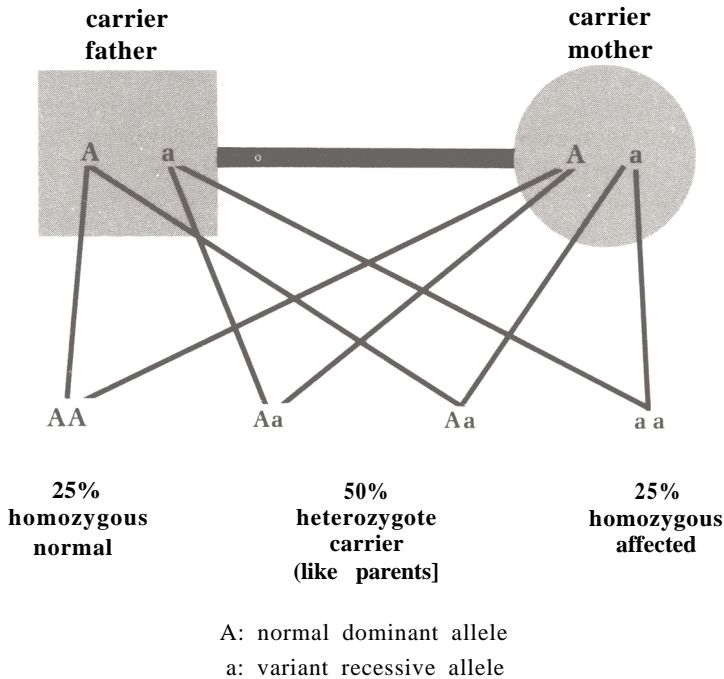
**Monogenic Disorders.** People possess two copies of each gene, one from the mother and one from the father. The various forms of a gene at any particular location on a chromosome are known as **alleles**. In addition to a gene’s normal form, variant alleles can occur through mutation; mutations that are not lethal are then passed on to future generations. When the two copies of a particular gene are the same, the individual is termed **homozygous** for that gene; when the alleles are different, the individual is **heterozygous**.

**Autosomal recessive.** Sometimes the existence of a single variant gene does not cause any abnormality in an individual’s functioning because the necessary “instructions” for the functioning of the cell are supplied by the other, normal gene. The presence of a variant gene leads to a disease only when it occurs on both autosomes in a pair; in other words, when both parents contribute genetic material containing the same variation, their child is homozygous for that variant form of the gene.<sup>1</sup> A genetic disorder that occurs in this fashion is termed **autosomal recessive**. Cystic fibrosis, phenylketonuria (PKU), Tay-Sachs disease, and sickle-cell anemia are examples of autosomal recessive conditions. Many other human characteristics besides those termed diseases are also inherited in a recessive fashion. For example, the ability to taste the organic compound phenylthio-urea is inherited in this way. The substance is intensely bitter to those who can detect it, but one individual in four is unable to taste it. In the case of a recessive **disease**, the variant allele is not expressed and the normal allele dominates.

A heterozygote for a particular variant gene is sometimes termed a “carrier” for the condition associated with that variant gene because he or she does not manifest the disease but is capable of passing the variant gene to offspring. If two carriers mate, each child they have has a 25% chance of having two abnormal genes (and, thus, of having the condition), a 50%

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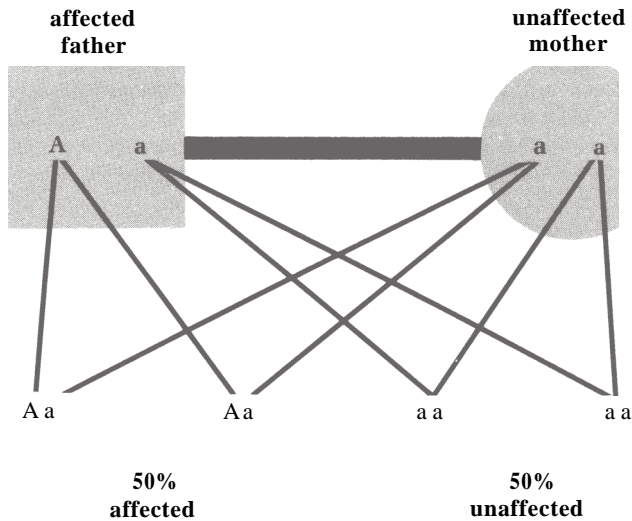
<sup>1</sup> Usually, both parents would be heterozygotes; if the disease is not a lethal one, a parent could be a homozygote him or herself. Alternatively, the parent may not have the abnormal gene in his or her own somatic cells, but it may have occurred in the germ cell as a new mutation.

**Figure B1: Autosomal Recessive Inheritance**

chance of being an unaffected carrier, and a 25% chance of not having the abnormal gene in question (see Figure B-1).

**Autosomal dominant.** Some variant genes are **dominant**, that is, their effects are expressed even if their allele on the paired chromosome is normal. Consequently, people manifest autosomal dominant disorders even if they have only one variant allele in the relevant pair. “Carriers”—who would typically be affected by the disorder themselves—can pass on an autosomal dominant disorder even if their mates do not carry the same variant gene. A couple in which one person is a carrier (a heterozygote with one variant dominant allele and one normal recessive allele) and the other person is a homozygote (with two recessive normal alleles) has a 50% chance with each pregnancy of having a child with an autosomal dominant disorder and a 50% chance of having an unaffected child (see Figure B-2). Huntington’s disease, achondroplastic dwarfism, and polycystic kidney disease are examples of autosomal dominant disorders.

**X-linked recessive.** An X-linked recessive disorder is caused by a variant recessive allele on the X chromosome. These disorders occur most frequently in males; because males have only one X chromosome, a variant gene on that chromo-

**Figure B2: Autosomal Dominant Inheritance\***

A: variant dominant allele  
a: normal recessive allele

\*Either parent could be affected. In this example, the father is affected.

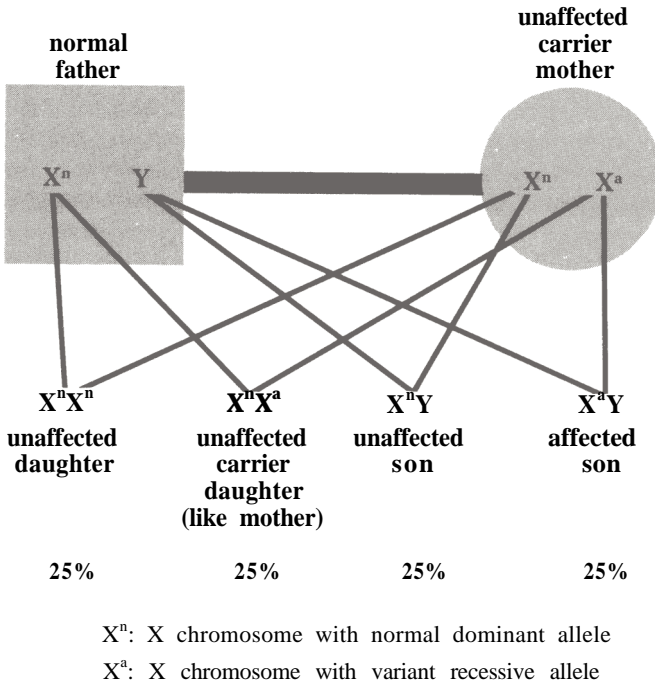
some cannot be “hidden” by a dominant normal gene on the other chromosome of the pair. Since females usually have two X chromosomes, they are unlikely to have X-linked recessive disorders; the normal gene on the second X chromosome dominates and supplies the genetic information necessary for normal functioning.<sup>2</sup> The sons of women who are carriers of a variant X-linked recessive allele have a 50% chance of having the disorder; the daughters of such women have a 50% chance of being unaffected carriers, like their mothers (see Figure B-3). Hemophilia is an example of an X-linked recessive disorder.

**X-linked dominant.** In X-linked dominant conditions, the variant allele on the X chromosome is dominant over the normal allele. Therefore, a heterozygous woman with only one variant allele would be affected, as would all males who inherited the variant allele. X-linked dominant conditions are rare. Vitamin-D resistant rickets is an example of a disease with this inheritance pattern.

**Multifactorial Disorders.** “Multifactorial” disorders result from interactions among numerous genes and environmental

<sup>2</sup> A female will have an X-linked recessive disorder only when she receives one variant X from her mother (who is probably unaffected) and another from her father, either through a germinal mutation or because he was affected by the variant gene.

**Figure B3: X-Linked Recessive Inheritance**



factors. According to a widely accepted “threshold” theory, a certain number of causative alleles must be present to place an individual “at risk” for a multifactorial disorder; in the case of birth defects, an environmental interaction at a specific time in development is also required for the disorder to be expressed. Because family members share many of the same genes, relatives of an individual with a multifactorial disorder are at an increased risk for having the “threshold” number of causative alleles, and may be exposed to similar environmental influences. Thus, the risk for first-degree relatives is greater because they share more of the same alleles than second-degree relatives do, who in turn are at greater risk than third-degree relatives, and so on. Examples of multifactorial disorders with substantial genetic causation are neural tube defects, cleft lip with or without cleft palate, and club foot.

**Chromosomal Defects.** A deviation in the amount of chromosomal material typically leads to abnormalities. There are several types of deviations—termed **aneuploidies**—involving too many or too few chromosomes. They include **trisomies** (when there are three copies of a particular chromosome rather than two) and **monosomies** (when one chromosome in a pair is missing). Rearrangements of portions of chromosomes are



termed **translocations, inversions, deletions, and additions**. An individual who carries a chromosomal rearrangement in which genetic material that is missing on one chromosome has been **balanced** by the translocation of the same material on another chromosome is usually clinically normal. Such a person, however, has a higher than normal risk of having miscarriages or of giving birth to a child with a variant chromosome pattern because during meiosis too much or too little chromosomal material may be passed on to any particular germ cell.

Down syndrome, the most common cause of mental retardation, is characterized by an extra number 21 chromosome. Thus, individuals with Down syndrome (also called trisomy-21) usually have cells containing 47 rather than 46 chromosomes. Most cases arise because of spontaneous mutations during the production of germ cells or early in the cellular development after fertilization, even though the parents have a normal chromosomal pattern. Couples with a child with Down syndrome of this type face a somewhat higher risk than the rest of the population of having a second child with the condition. Sometimes, however, one parent has a balanced translocation, and meiosis results in a germ cell containing extra chromosomal fragments. In this case, the parents clearly have a higher than average risk of recurrence of the disorder in future pregnancies.

Most chromosomal abnormalities of the autosomes cause serious and widespread defects that are clinically apparent in infancy. In contrast, abnormalities of the sex chromosomes tend to be much less obvious; in fact, they may go undiagnosed until adolescence or adulthood. An example of this condition is Klinefelter syndrome.

**Genetic Heterogeneity.** Some disorders or defects actually may stem from a variety of sources, genetic and nongenetic. For example, retinitis pigmentosa, a rare disorder affecting the eye, can be inherited as an autosomal recessive, an autosomal dominant, or an X-linked recessive disorder. Consequently, risk estimates for future pregnancies must always consider whether the disorder could be inherited in more than one way.



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# The Commission's Process

C

## Former Commissioners

These members served on the Commission while this study was being conducted; their terms of service, which were completed before the Report was approved, are indicated in parentheses.

- Renée C. Fox (July 1979-Feb. 1982)  
Mario Garcia-Palmieri (July 1979-Aug. 1982)  
Frances K. Graham (May 1980-Jan. 1982)  
Albert R. Jonsen (July 1979-Aug. 1982)  
Patricia A. King (July 1979-May 1980)  
Mathilde Krim (July 1979-Oct. 1981)  
Donald N. Medearis (July 1979-Feb. 1982)  
Anne A. Scitovsky (July 1979-Aug. 1982)  
Carolyn A. Williams (Sept. 1980-Aug. 1982)

## Commission Hearings

**May 8, 1981**

### **Aims, Methods and Issues of Genetic Screening**

Dr. Barton Childs, Professor of Pediatrics, Johns Hopkins  
University School of Medicine

### **Public Policy Issues in Screening**

Dr. Michael Kaback, Professor of Pediatrics and Medicine,  
University of California at Los Angeles School of  
Medicine

Dr. Robert F. Murray, Jr., Professor of Pediatrics, Medicine, and Oncology, Howard University College of Medicine

Dr. Claire O. Leonard, Assistant Professor of Pediatrics and Obstetrics-Gynecology, Johns Hopkins University School of Medicine

### **Screening for Cystic Fibrosis**

Dr. Robert J. Beall, National Director, Cystic Fibrosis Foundation

Dr. Richard W. Erbe, Medical Genetics Unit, Massachusetts General Hospital

Doris F. Tulcin, President, Cystic Fibrosis Foundation

Georgette Weaver, Board of Directors, Florida Chapter, Cystic Fibrosis Foundation

Dr. Norman C. Fost, Associate Professor of Pediatrics and History of Medicine, University of Wisconsin

### **March 12, 1982**

#### **Review of Staff Draft with Panel**

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Dr. Audrey Manley, Director of Genetic Services Programs, Office of Maternal and Child Health. U.S. Department of Health and Human Services

### **Public Comment**

Dr. Olga Fairfax, Founder, United Methodists for Life

### **May 14-15, 1982**

#### **Commission Deliberation on Draft Report**

Richard Vodra, Public Policy Director, Cystic Fibrosis Foundation

Sherry Keramedes, Ph.D. Assistant Medical Director, Cystic Fibrosis Foundation

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