REVIEW ARTICLE

GENOMIC MEDICINE

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Population Screening in the Age of Genomic Medicine

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Physicians in the era of genomic medicine will have the opportunity to move from intense, crisis-driven intervention to predictive medicine. Over the next decade or two, it seems likely that we will screen entire populations or specific subgroups for genetic information in order to target interventions to individual patients that will improve their health and prevent disease. Until now, population screening involving genetics has focused on the identification of persons with certain mendelian disorders before the appearance of symptoms and thus on the prevention of illness[1] (e.g., screening of newborns for phenylketonuria), the testing of selected populations for carrier status, and the use of prenatal diagnosis to reduce the frequency of disease in subsequent generations (e.g., screening to identify carriers of Tay–Sachs disease among Ashkenazi Jews). But in the future, genetic information will increasingly be used in population screening to determine individual susceptibility to common disorders such as heart disease, diabetes, and cancer. Such screening will identify groups at risk so that primary-prevention efforts (e.g., diet and exercise) or secondary-prevention efforts (early detection or pharmacologic intervention) can be initiated. Such information could lead to the modification of screening recommendations, which are currently based on population averages (e.g., screening of people over 50 years of age for the early detection of colorectal cancer).[2]

In this review, we describe current and evolving principles of population screening in genetics. We also provide examples of issues related to screening in the era of genomic medicine.

Principles of Population Screening

The principles of population screening developed in 1968 by Wilson and Jungner[3] form a basis for applying genetics in population screening. These principles emphasize the importance of a given condition to public health, the availability of an effective screening test, the availability of treatment to prevent disease during a latent period, and cost considerations. Wald outlined three elements of screening: the identification of persons likely to be at high risk for a specific disorder so that further testing can be done and preventive actions taken, outreach to populations that have not sought medical attention for the condition, and follow-up and intervention to benefit the screened persons.[4] Several groups have used these principles to develop policies regarding genetic testing in populations.[5] Screening of newborns, which has been carried out in the United States since the early 1960s, serves as a foundation for other types of genetic screening.[6,7]

NEWBORN SCREENING

Each state (and the District of Columbia) determines its own list of diseases and methods for the screening of newborns. Only phenylketonuria and hypothyroidism are screened for by all these jurisdictions.[7] Table 1 lists the disorders that are included in many state programs for newborn screening and gives one an idea of the diversity of techniques employed. The addition of a test or a method to a state's screening program depends on the efforts of advisory boards for newborn screening, political lobbying of legislatures, and the efforts of laboratory personnel for newborn screening. There has often been a lack of research to demonstrate the effectiveness of screening and treatment for a disorder, either before or after the disease is added to the newborn-screening program. The technological spectrum ranges from the original Guthrie bacterial inhibition assay, developed in the late 1950s,[8] to tandem mass spectrometry[9,10] and DNA analysis.[11-13] With the use of DNA testing of the blood blot obtained from the screening of a newborn, the state of Texas reduced the age at confirmation of the diagnosis of sickle cell disease from four months to two months.[14] Rapid diagnostic confirmation is imperative for the initiation of penicillin prophylaxis to prevent illness and death in patients with sickle cell disease.[15,16] The cost of this follow-up test is $10 or less for each positive sample from the original screening.[14]

Two-tiered testing is also used for congenital hypothyroidism, since patients with primary hypothyroidism have elevated levels of thyrotropin and low levels of thyroxine.[17,18] The two-tiered strategy provides better sensitivity and specificity than either test alone. However, the health care professional needs to use clinical judgment in addition to the results of newborn screening. If a patient with a negative newborn-screening test has symptoms of congenital hypothyroidism, clinical acumen should override the test result and specific diagnostic testing should be performed.[17] The results of screening tests are not infallible because of the possibility of biologic, clerical, and laboratory errors.[19-21]

Audiometry is used to screen newborns for hearing defects. The frequency of deafness in childhood is as high as 1 in 500.[22] These programs are based

Table 1. Disorders Included in Newborn-Screening Programs.

Disorder	Screening Method	States Offering Test	Treatment
Phenylketonuria	Guthrie bacterial inhibition assay Fluorescence assay Amino-acid analyzer Tandem mass spectrometry	All	Diet restricting phenylalanine
Congenital hypothyroidism	Measurement of thyroxine and thyrotropin	All	Oral levothyroxine
Hemoglobinopathies	Hemoglobin electrophoresis Isoelectric focusing High-performance liquid chromatography Follow-up DNA analysis	Most	Prophylactic antibiotics Immunization against *Diplococcus pneumoniae* and *Haemophilus influenzae*
Galactosemia	Beutler test Paigen test	Limited no.	Galactose-free diet
Maple syrup urine disease	Guthrie bacterial inhibition assay	Limited no.	Diet restricting intake of branched-chain amino acids
Homocystinuria	Guthrie bacterial inhibition assay	Limited no.	Vitamin B_{12} Diet restricting methionine and supplementing cystine
Biotinidase deficiency	Colorimetric assay	Limited no.	Oral biotin
Congenital adrenal hyperplasia	Radioimmunoassay Enzyme immunoassay	Limited no.	Glucocorticoids Mineralocorticoids Salt
Cystic fibrosis	Immunoreactive trypsinogen assay followed by DNA testing Sweat chloride test	Limited no.	Improved nutrition Management of pulmonary symptoms

in hospitals and are therefore decentralized.[7] Mutations in the gene for connexin 26 account for 40 percent of all cases of childhood hearing loss, with a carrier rate of 3 percent in the population.[23] A single mutation is responsible for most of these cases in a mixed U.S. population.[23] A different mutation is predominant among Ashkenazi Jews.[24] Two-tiered testing in which audiometry is followed by DNA testing for mutations in the connexin 26 gene may be a useful and cost-effective approach to screening for hearing loss.[25] Early detection provides the possibility of aggressive intervention to improve a child's language skills, provide cochlear implants, or do both.[23]

In 1999, the American Academy of Pediatrics and the Health Resources and Services Administration convened the Newborn Screening Task Force to address the lack of consistency in the disorders included in screening programs and the testing methods used in the various states.[26] The group concluded that there should be a national consensus on the diseases tested for in state programs of newborn screening. The American Academy of Pediatrics, American College of Medical Genetics, Health Resources and Services Administration, Centers for Disease Control and Prevention, March of Dimes, and other groups are working together to create a national agenda for newborn screening.

A disorder that may be included in newborn screening tests is cystic fibrosis. Cystic fibrosis has been included in the newborn-screening program in Colorado since the demonstration that some affected infants had malnutrition as a result of the pancreatic dysfunction.[27] This observation was confirmed by a randomized trial in Wisconsin involving infants with a positive newborn-screening test for cystic fibrosis.[28] In the study, infants with a positive test were randomly assigned to a screened group (in which physicians were informed of the positive screening result) or a control group (in which physicians were informed of the positive screening result when the child was four years of age if cystic fibrosis had not been diagnosed clinically or if the child's parents had not asked about the results of the screening test). In Wisconsin, infants are first tested with the use of an immunoreactive trypsinogen assay[29]; if the result is positive, the test is followed up with a DNA test of the original specimen of dried blood obtained for newborn screening.[30-32] The cost of each follow-up DNA test for infants with positive results on the immunoreactive trypsinogen assay was estimated to be $3 to $5.[31]

A new form of technology, tandem mass spectrometry, detects more than 20 disorders, not all of which can be treated. A justification for introducing tandem mass spectrometry is the identification of newborns with medium-chain acyl–coenzyme A (CoA) dehydrogenase deficiency (Fig. 1). Without early detection and intervention, this deficiency leads to episodic hypoglycemia, seizures, coma associated with intercurrent illnesses and fasting, and a risk of death of approximately 20 percent after the first episode in the first and second year of life.[33,34] Management of medium-chain acyl–CoA dehydrogenase deficiency involves educating families about the dangers of hypoglycemia, which can be triggered by fasting, with resulting fat catabolism, during intercurrent illnesses and by inadequate caloric intake, and of the need for aggressive intervention with intravenous glucose if hypoglycemia does occur. For many of the other disorders detected by tandem mass spectrometry, treatment is not available, but families will potentially be spared "diagnostic odysseys" with a severely ill child.[35] The eventual goal is collaborative research to determine the appropriate treatment after early diagnosis.[7,36] In addition, this information may be useful for genetic counseling of these families. A cause for concern is that tandem mass spectrometry may detect metabolic variations of unknown clinical significance, creating unwarranted anxiety in parents and health care professionals.

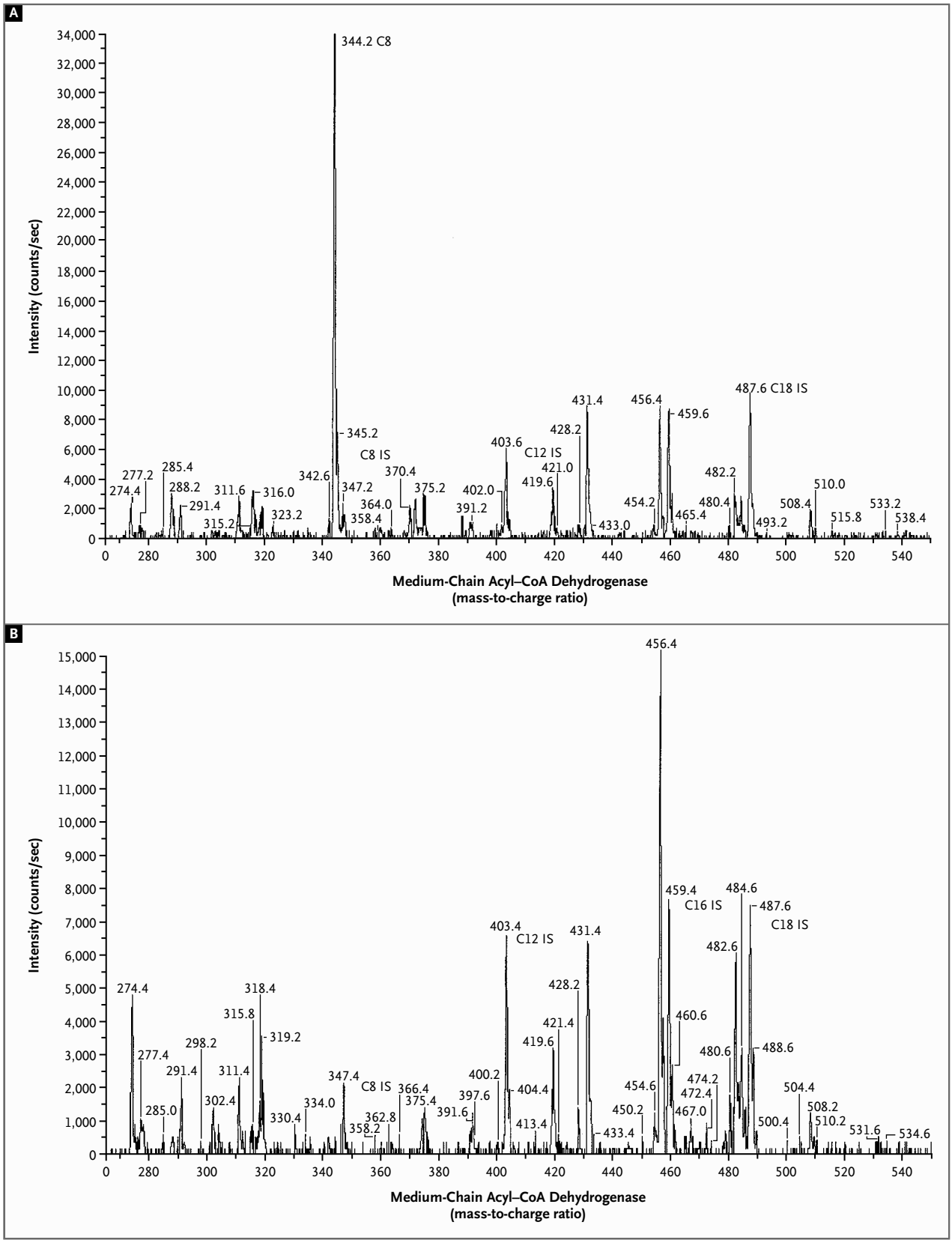
CARRIER SCREENING OF ADULT POPULATIONS FOR SINGLE-GENE DISORDERS

TAY–SACHS DISEASE

Carrier screening for Tay–Sachs disease has targeted Ashkenazi Jewish populations of childbearing age.[37] In a 30-year period, 51,000 carriers have been identified, resulting in the identification of 1400 two-carrier couples.[37] Another approach has been taken in Montreal, where high-school students learn about Tay–Sachs disease and thalassemia as part of a biology course. Those of Ashkenazi Jewish descent

Figure 1 (facing page). Results of Screening by Tandem Mass Spectrometry for Medium-Chain Acyl–Coenzyme A (CoA) Dehydrogenase Deficiency in an Affected Patient (Panel A) and a Control Subject (Panel B).

IS denotes internal standard. (Figure provided courtesy of John E. Sherwin, Ph.D.)



can request carrier testing for Tay–Sachs disease, and those of Mediterranean ancestry can be tested for thalassemia.[38] When women who have been identified as carriers in high school later consider becoming pregnant, they bring their partners in for testing. Although this program has been very successful in Canada, the culture and the legal environment in the United States, including a standard that does not allow high-school students to consent to medical care and the implications for insurability, may prohibit the adoption of such a model.[39]

CYSTIC FIBROSIS

Northern Europeans have a carrier frequency of cystic fibrosis of 1 in 25 to 1 in 30; the rate is lower in other ethnic and cultural groups.[17] A 1997 National Institutes of Health Consensus Development Conference[40] recommended that the following populations be screened for mutations associated with cystic fibrosis: the adult family members of patients with cystic fibrosis, the partners of patients with cystic fibrosis, couples planning a pregnancy, and couples seeking prenatal care. Since more than 900 different mutations associated with cystic fibrosis have been reported in the literature,[41] the establishment of screening programs has been difficult. However, the American College of Medical Genetics, the American College of Obstetricians and Gynecologists, and the National Institutes of Health agreed that mutations with a carrier frequency of at least 0.1 percent in the general population should be screened for, resulting in a panel of 25 mutations recommended for carrier testing.[42] These guidelines suggest that carrier testing should be offered to all non-Jewish white persons and Ashkenazi Jews and that other ethnic and cultural groups should be informed of the limitations of the panel to detect carriers in their group (in the case of black persons) or of the low incidence of cystic fibrosis in their group (in the cases of Asian and Native American persons).

Mutations in the gene associated with cystic fibrosis have also been associated with obstructive azoospermia in men[43] and with chronic rhinosinusitis.[44,45] The guidelines recommend including in the screening panel a test for the R117H mutation, which is associated with congenital bilateral absence of the vas deferens.[42] If the R117H mutation is found, further testing and genetic counseling are recommended.[42]

POPULATION SCREENING FOR GENETIC SUSCEPTIBILITY TO COMMON DISEASES

Several groups have recently addressed the value of population screening for genetic susceptibility to conditions with onset in adulthood.[46-48] Table 2 presents a synthesis of the suggested modifications to the 1968 criteria,[3] based on current principles.

Hereditary hemochromatosis and the thrombophilia that results from carrying a single copy of a factor V Leiden gene are two adult-onset illnesses to which the suggested revised principles for population screening would apply (Table 2), and these illnesses also reflect the complex scientific and social issues involved in screening for risk factors for disease. As shown by Wald et al.,[49] screening for risk factors for nondiscrete traits that are distributed continuously may not be beneficial even if the factors are associated with a high risk of disease (e.g., high cholesterol levels and heart disease). This is because risk factors are determined by comparing the probability of disease at each end of the distribution of the risk factor (those with the highest level of risk and those with the lowest level of risk). Those with a moderate level of risk are not considered. The likelihood of a disorder, given a positive screening result, is expressed relative to the average risk of the entire population. The goal of screening is to identify individual persons with a high risk in comparison to everyone else.

HEREDITARY HEMOCHROMATOSIS

Many consider hereditary hemochromatosis to be the key example of the need for population screening in the genomic era,[50] but gaps in our knowledge preclude the recommendation of population screening for this disorder. This policy issue was discussed by an expert-panel workshop held by the Centers for Disease Control and Prevention and the National Human Genome Research Institute.[51] The panel concluded that population genetic testing for mutations in *HFE*, the gene for hereditary hemochromatosis, could not be recommended because of uncertainty about the natural history of the disease, age-related penetrance, optimal care for persons without symptoms who are found to carry mutations, and the psychosocial impact of genetic testing.[52,53] On the other hand, mutation analysis may be useful in confirming the diagnosis of hereditary hemochromatosis in persons with abnormal indexes of iron metabolism. A meta-analysis of studies[54]

showed that homozygosity for the C282Y mutation was associated with the highest risk of hereditary hemochromatosis. The risks associated with other genotypes, including C282Y/H63D and H63D/H63D, were much lower. A recent large cohort study in the Kaiser Permanente Southern California health care network suggests that the disease penetrance for *HFE* mutations may be quite low.[55] Only 1 of the 152 subjects who were homozygous for C282Y had symptoms of hereditary hemochromatosis.

Several questions remain regarding the benefits and risks of identifying and treating persons without symptoms who are at high risk for hereditary hemochromatosis (i.e., through population screening). This process should be clearly distinguished from early case finding, which could include testing of iron status, and analysis for mutations in *HFE*, in persons who present with clinical symptoms consistent with a diagnosis of hereditary hemochromatosis. The natural history of hereditary hemochromatosis — particularly age-related penetrance — remains unknown. Despite the relatively high prevalence of the two most common mutations in the U.S. population,[56] questions persist regarding the nature and prevalence of mutations in specific ethnic and cultural groups, as well as the morbidity[57] and mortality[58] associated with this disease. Therefore, questions remain concerning the persons most likely to benefit from early treatment and thus about the optimal timing of screening and effective intervention, as well as ethical and psychosocial issues[59] (Table 2).

Table 2. Principles of Population Screening as Applied to Genetic Susceptibility to Disease.*

Public health assessment
The disease or condition should be an important public health burden to the target population in terms of illness, disability, and death.
The prevalence of the genetic trait in the target population and the burden of disease attributable to it should be known.
The natural history of the condition, from susceptibility to latent disease to overt disease, should be adequately understood.
Evaluation of tests and interventions
Data should be available on the positive and negative predictive values of the test with respect to a disease or condition in the target population.
The safety and effectiveness of the test and accompanying interventions should be established.
Policy development and screening implementation
Consensus regarding the appropriateness of screening and interventions for people with positive and negative test results should be based on scientific evidence.
Screening should be acceptable to the target population.
Facilities should be available for adequate surveillance, prevention, treatment, education, counseling, and social support.
Screening should be a continual process, including pilot programs, evaluation of laboratory quality and health services, evaluation of the effect of screening, and provisions for changes on the basis of new evidence.
The cost effectiveness of screening should be established.
Screening and interventions should be accessible to the target population.
There should be safeguards to ensure that informed consent is obtained and the privacy of those tested is respected, that there is no coercion or manipulation, and that those tested are protected against stigmatization and discrimination.

* Principles are based on Wilson and Jungner,[3] Goel,[46] Khoury et al.,[47] and Burke et al.[48]

FACTOR V LEIDEN

Factor V is an important component of the coagulation cascade leading to the conversion of prothrombin into thrombin and the formation of clots.[60] In factor V Leiden, the triplet coding for arginine (CGA) at codon 506 is replaced by CAA, which codes for glutamine (R506Q), resulting in thrombophilia or an increased propensity for clot formation.[61] The prevalence of factor V Leiden varies.[62,63] Among persons of northern European descent, the prevalence is about 5 percent. The highest prevalence of factor V Leiden is found in Sweden and in some Middle Eastern countries; it is virtually absent in African and Asian populations. Heterozygosity for factor V Leiden results in an increase in the incidence of venous thrombosis by a factor of 4 to 9.[64,65]

An interaction between factor V Leiden and the use of oral contraceptives was originally found in a case–control study of risk factors for venous thrombosis.[66] Although the use of oral contraceptives alone increases the risk of venous thrombosis by a factor of about 4 and the presence of factor V Leiden alone increases the risk by a factor of about 7, their joint effect was an increase by a factor of more than 30. In spite of the high relative risk, the absolute risk was relatively low (about 28 per 10,000 person-years) among women with factor V Leiden who used oral contraceptives, because the incidence of this complication is relatively low in the population.

The question of whether it is beneficial to screen women for factor V Leiden before prescribing oral contraceptives remains controversial. Venous thrombosis is relatively rare, and the mortality associated with venous thrombosis is low among young women.[67] More than half a million women would need to be screened for factor V Leiden — resulting in tens of thousands of women being denied prescriptions for oral contraceptives — to prevent a single death. In addition to medical and financial considerations, there are issues related to the quality of life, the risk of illness and death from unwanted pregnancy, and concern about possible discrimination by insurance companies. In 2001,

the American College of Medical Genetics stated that the opinions and practices regarding testing for factor V Leiden vary considerably, and no consensus has emerged.[68]

For the individual healthy woman contemplating the use of oral contraceptives, the risk–benefit equation does not currently favor screening. For women without symptoms who have family histories of multiple thrombosis, there are no evidence-based guidelines, and decisions will have to be reached individually, without reliance on population-based recommendations.

These examples show why it is essential that data continue to be analyzed to inform decision making for individual persons and populations.

ETHICAL, LEGAL, AND SOCIAL ISSUES

The following are among the ethical, legal, and social issues involved in population-based screening that confront health care providers, policymakers, and consumers.

TESTING CHILDREN FOR ADULT-ONSET DISORDERS

Two committees of the American Academy of Pediatrics have recently addressed the issue of molecular genetic testing of children and adolescents for adult-onset disease.[69,70] The Committee on Genetics[69] recommended that persons under 18 years of age be tested only if testing offers immediate medical benefits or if another family member benefits and there is no anticipated harm to the person being tested. The committee regarded genetic counseling before and after testing as an essential part of the process.

The Committee on Bioethics[70] agreed with the Newborn Screening Task Force[27] that the inclusion of tests in the newborn-screening battery should be based on evidence and that there should be informed consent for newborn screening (which is currently not required in the majority of states). The Committee on Bioethics did not support the use of carrier screening in persons under 18 years of age, except in the case of an adolescent who is pregnant or is planning a pregnancy. It recommended against predictive testing for adult-onset disorders in persons under 18 years.

UNANTICIPATED INFORMATION

Misattribution of Paternity

The American Society of Human Genetics has recommended that family members not be informed of misattributed paternity unless determination of paternity was the purpose of the test.[71] However, it must be recognized that such a policy may lead to misinformation regarding genetic risk.

Unexpected Associations among Diseases

In the course of screening for one disease, information regarding another disease may be discovered. Although the person may have requested screening for the first disorder, the presence of the second disorder may be unanticipated and may lead to stigmatization and discrimination on the part of insurance companies and employers. Informed consent should include cautions regarding unexpected findings from the testing.

OVERSIGHT AND POLICY ISSUES

In 1999, the Secretary's Advisory Committee on Genetic Testing was established to advise the Department of Health and Human Services on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests (http://www4.od.nih.gov/oba/sacgt.htm).[72] The committee conducted public outreach to identify issues regarding genetic testing. There was an overwhelming concern on the part of the public regarding discrimination in employment and insurance. The advisory committee recommended the support of legislation preventing discrimination on the basis of genetic information and increased oversight of genetic testing. The Food and Drug Administration was charged as the lead agency and was urged to take an innovative approach and consult experts outside the agency. The goal is to generate specific language for the labeling of genetic tests, much as drugs are described in the *Physicians' Desk Reference*.[73] Such labeling would provide persons considering, and health professionals recommending, genetic tests with information about the clinical validity and value of the test — what information the test will provide, what choices will be available to people after they know their test results, and the limits of the test.

In conclusion, although the use of genetic information for population screening has great potential, much careful research must be done to ensure that such screening tests, once introduced, will be beneficial and cost effective.

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