APPENDIX 6. SCIENTIFIC ADVANCES AND SOCIAL RISKS: HISTORICAL PERSPECTIVES OF GENETIC SCREENING PROGRAMS FOR SICKLE CELL DISEASE, TAY-SACHS DISEASE, NEURAL TUBE DEFECTS AND DOWN SYNDROME, 1970-1997*

Final Report of the Task Force on Genetic Testing

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INTRODUCTION

Scientific research on the genetic basis of human disease has made breathtaking progress over the past several decades, providing an enormous increase in genetic tools for diagnosis, and also posing critical, confounding problems. This essay will historically analyze three genetics testing programs over the past quarter century in order to elucidate some of these problems, and help in developing genetics screening policies that are ethical and effective.

Public assessments of new genetic research have predicted a vast array of diagnostic and therapeutic technologies by the close of the twentieth century.› Of course it is not possible to forecast just how many pathological conditions will be genetically diagnosed or treated in the next millennium, but physicians, epidemiologists, public health professionals, insurance companies, and patients, to name a few, will have strikingly more genetically based tools available to them. In principal, these tools and the mass screening programs that may be developed from them will facilitate informed reproductive decisions and, when possible, allow physicians to treat and prevent disease.

Exuberance over this progress has been tempered by a growing set of questions: Scientifically, will testing for genetic susceptibility to common complex disorders be sufficiently sensitive, and will it have enough positive predictive value to gain wide acceptance as a predictor of those at risk of future disease? Will these exciting new technologies be sabotaged by the serious medical, psychological, ethical, and legal problems that may be associated with them?

Previous applications of genetic theories to social and public health policies in American history suggest that cultural attitudes toward illness and abnormality run deep. They may force themselves into the debate about how best to apply and interpret genetic screening and therapeutic technologies. There are a number of other issues:

race, ethnicity, and gender can affect the understanding of genetic disease; patients, physicians, and genetic counselors must know how to interpret test results; laboratory accuracy and validity data are vital; family members are affected by test outcomes; confidentiality is particularly essential; predictive tests may seriously impact a patient's health and life insurance, and ethical dilemmas arise when the only prevention of some genetic diseases is termination of a pregnancy.

These significant problems may not be considered by the scientist at the laboratory bench or the well-intentioned health care provider who orders a genetic test.

History is, at best, a less-than-perfect approximation of the present, let alone of the future. But its analysis does provide a means to consider events from earlier genetic screening programs that may have become both culturally embedded and actively present in current social responses. In particular, this essay will discuss the social historical contexts of three applications of genetic screening tools to the diagnosis of disease in the United States during the past quarter century: 1) the Sickle Cell Anemia (SCA) screening programs of the early 1970s; 2) the Tay-Sachs disease (TS) screening programs of the same era; and 3) the maternal alpha-fetoprotein (AFP) prenatal screens for neural tube defects and Down syndrome which began to be mass-marketed during the 1980s.

SICKLE CELL DISEASE AND THE AFRICAN-AMERICAN POPULATION, 1970-1975:

THE RELATIONSHIP OF RACE AND GENETIC DISEASE

It is difficult to pinpoint exactly why a collection of public health agencies, physicians, African-American activists, and the Federal and several state governments chose, from all the pressing medical and socioeconomic needs of the African-American community during the early 1970s, to focus on the implementation of mandatory sickle cell screening laws. Even now there is no definitive curative treatment for sickle cell anemia, a disease that affects one out of every 400 to 600 African Americans, or 0.2 percent of that population. (One out of every 10 to 12 African- Americans are carriers of the trait.)

The majority of those screened for sickle cell in the early 1970s were school-aged children or young adults. If any of these individuals actually had sickle cell disease, they probably already had been clinically diagnosed. Because there was no definitive treatment to prevent damage, they were highly likely to have already been harmed. Nor, at that time, was there any safe and inexpensive means of making a prenatal diagnosis of sickle cell anemia in the developing fetus. (It was not until 1978 that Y. W. Kan developed the DNA limited marker test.) Since prenatal diagnosis was virtually not possible, and there were no curative therapies, what did the early sickle cell screening programs hope to accomplish? As Holtzman observed, the "compelling public health interest served by these laws is difficult to discern."

The early 1970s coincided with the peak of the Civil Rights movement, wider voter registration among African Americans, an increase in the number of African-American elected officials, and African-American activism ranging from that of clergy and church-based groups to the Black Panthers.[3] In response to the maelstrom of social forces then engulfing the African-American community, President Richard Nixon issued a number of executive orders. A presidential initiative in 1971 increased federal support for the treatment of and research on, sickle cell anemia (approximately $6 million a year). That same year, U.S. Senate hearings on the establishment of a national sickle cell anemia program were initiated. Between 1970 and 1972, twelve states and the District of Columbia enacted mandatory sickle cell screening laws for African-American citizens. More often than not, however, these laws were written and passed without adequate attention to the stigmatizing of not only those

people with the disease, but also of those who carried the sickle cell trait. As Reilly concluded in his analysis of the early sickle cell programs: "In retrospect it is clear that the haste with which these laws were drafted and passed contributed substantially to the acrimonious controversy that soon engulfed screening practices."

Several major criticisms of the early sickle cell screening programs have been identified. These criticisms include: 1) a lack of sensitivity to issues of race; 2) controversy surrounding the accuracy and validity of the early screening tests; and 3) inadequate protection of the patient's rights.

Race and Genetics. The most serious criticism of the early sickle cell screening programs has to do with the racial issues surrounding the disease. The initial programs were directed almost exclusively at African-Americans. The briefest review of some of the laws mandating these programs supports that a specific net was cast for African Americans. For example, the New York State law ordered that all persons "not of the Caucasian, Indian, or Oriental races" be tested for sickle cell trait before being allowed to obtain a marriage license. A subsequent New York State law required all urban (but not suburban or rural) schoolchildren to be screened with the tacit understanding that the overwhelming majority of African Americans living in New York at that time were urban dwellers. A similar law enacted in the District of Columbia went one step further in the process of genetic isolation by referring to the blood dyscrasia as a "communicable disease," a term traditionally reserved for infectious rather than inherited diseases and implying the need for quarantine or ostracism.[7]

The compulsory screening laws directed at only African Americans obscured the fact that ethnic groups other than blacks can carry the trait and suffer from sickle cell anemia (e.g., people of Mediterranean origins), an omission that ethicist John Fletcher characterized as "racial obfuscation." The national focus on a relatively rare genetic disease presented as "the most vital health issue" facing African Americans also presented several extremely negative political implications—a situation which was not lost on the black community.[8] For example, Bryant Rollins, the executive editor of the Amsterdam News (New York City), noted that the federal government's award of a five-year $2.5 million grant to the Harlem Hospital for sickle cell research was far from ideal: "If you read the fine print, there is another side to this grant, the effect of which is to rob the Harlem community of $1 million in much needed funds" that might be better applied to the myriad social, economic, and health problems affecting it.*

Misinterpretation of Test Results. A second criticism of the initial sickle cell screening programs was the potential for misinterpretation of the results. At some centers, the validity of the screening methods themselves became the subject of controversy. There were several documented reports of the misuse of the Sickledex test (which does not distinguish trait from homozygous affected) and of the poor quality of many of the laboratories performing the tests, sometimes under state mandates.[9] Many of the state and local programs were based on an inadequate knowledge of the genetics of sickle cell disease and as a consequence many of the laws needlessly stigmatized carriers of the sickle cell trait as well as those with the illness. Perhaps most glaring was the apparent ease with which the diagnosis of a heterozygote "carrier status" of sickle cell anemia was used almost interchangeably with homozygote "disease status."

The ostracism of sickle cell carriers, unfortunately, became far more than a theoretical concern for African Americans and public health officials. One especially outrageous diatribe by the late scientist and Nobel laureate Linus C. Pauling published in a February, 1968 issue of the UCLA Law Review reflects this stigmatization process of sickle cell carriers: "There should be tattooed on the forehead of every young person, a symbol showing possession of the sickle cell gene [so as to prevent] two young people carrying the same seriously defective gene in single dose from falling in love with one another."

More seriously, by the early 1970s many African Americans were stigmatized by their carrier status in the form of being denied health and life insurance, employment opportunities, and even acceptance into the U.S. Air Force Academy. The African-American community soon perceived the psychosocial risks of the sickle cell screening programs and many persons expressed anger at being further discriminated against for simply being a carrier of sickle cell trait.[9]

Inadequate education and counseling at many of the early screening programs only contributed to the milieu of confusion, stigma, and what Abraham Bergman and his colleagues called "sickle cell 'nondisease.'"[*,9] To make matters worse, many American physicians then were not well educated in the diagnosis and management of genetic diseases. For example, in a 1974 survey of 160 physicians' knowledge about sickle cell anemia, one in seven believed sickle cell trait to be indicative of a disease state; one in five found it difficult to clinically distinguish the trait from the disease, and one in two was unaware of the existence of the SC and the S-thal phenotypes.

Some community leaders responded by urging blacks to boycott the sickle cell screening programs. For example, in 1972, Ted Veal, a representative of the African-American activist group, the People's Health Council of New York, described the mandatory screening programs as "genocidal health practices" of the white medical establishment. Indeed, sickle cell screening programs of the early 1970s produced a negative label of disease for an easily identifiable social group that had a long history of being the victims of social discrimination. That made the screening markedly different and far more dangerous in a social context than those programs developed during the same time period for diseases without an ethnic or racial association.

Protection of the Patient's Rights. The third major objection to these early sickle cell screening programs was that in the rush to get the laws into print, many vital protective clauses were omitted, although we have since learned from hard experience to incorporate them. Features that might have tempered the harsh process of genetic stigmatization such as test result confidentiality, competent genetic counseling for people with the trait and the disease, adequate public education on issues of genetic diseases and carrier status, guaranteed medical benefits for those afflicted with sickle cell anemia, and uniform guidelines to ensure quality control of the testing and laboratory facilities were either not considered or were patently ignored by those drafting the original sickle cell legislation.[9]

The problems of this particular application of genetics to social policy began to be recognized soon after the enactment of the state laws described above. By late 1972, Congress passed the National Sickle Cell Anemia Control Act, which reflected a number of these concerns. Although these problems were not rectified immediately, the energetic efforts of the African-American and medical communities, in addition to numerous legislators, lawyers, and public policymakers, helped to modify and greatly improve use of sickle cell anemia screening technologies. For example, during the 1980s, it was found that newborn screening for sickle cell anemia was justified because of the ability of antibiotics to prevent serious and sometimes fatal infections in children with sickle cell anemia. In addition, newly developed pneumococcal vaccines have contributed to the reduction of early death due to susceptibility to pneumococcal infections. Many African-American parents recognized the value of the sickle cell newborn screen. Still, some clinicians continue to find evidence of fear and avoidance of all forms of sickle cell testing especially among those African-Americans with relatives who underwent testing during the 1970s. In a study conducted in Rochester, New York during the 1980s, less than half of the pregnant African-American women at risk of having affected fetuses utilized prenatal diagnosis technologies.

TAY-SACHS DISEASE AND THE ASHKENAZI JEWISH-AMERICAN COMMUNITY, 1970-1980: THE IMPORTANCE OF INCLUDING THE COMMUNITY IN SCREENING PROGRAMS

Genetic screening for Tay-Sachs disease began to be developed about the same time as the early sickle cell screening programs discussed above. Like sickle cell disease, Tay-Sachs was found to occur predominantly in one defined ethnic population—infants of Ashkenazi (East European) Jewish ancestry. Unlike sickle cell disease, however, which can vary greatly in clinical symptoms and severity from patient to patient, Tay-Sachs victims had no hope of productive life and faced irreversible and progressive neurodegeneration, dementia, and death during the first five years of life.[»] Indeed, given the state of the art in medical care for Tay-Sachs disease during this period, the soundest public health approach to the problem was avoiding the birth of the affected fetus.

Ashkenazi Jews and African Americans had very different experiences with their genetic testing. In the first place, the reproductive choices for Tay-Sachs disease were less ambiguous when compared to sickle cell anemia; prenatal diagnosis for Tay-Sachs was possible.[»] Then, too, there were striking social differences between them. The Jewish-American community was no stranger to discrimination, particularly in its relation to the application of genetic theory to social policy. Many of those enrolling in the Tay-Sachs screening programs of the 1970s were, literally, the grandchildren of the East European Jewish immigrants who were stigmatized during the 1920s and accused of importing inferior genes and "protoplasm" into the United States.[»] Yet with the passage of time and acquisition of the confidence of assimilation, Jewish-Americans of the 1970s generally expressed fewer fears of discrimination than their African-American counterparts when confronted with these new screening technologies. There were some, however, who did not support Tay-Sachs screening.[»]

This difference of perception may have been due to the social experiences of these two ethnic groups in the United States over the past two centuries. By the early 1970s, the lives of Jewish-Americans (both those originating from Germany and Eastern Europe) had, for the most part, markedly improved by all economic and social markers. Members of the African-American community, on the other hand, remained the target for a number of forms of discrimination and were actively fighting for basic civil rights. The latter group was particularly vulnerable to additional stigmatization in the form of a genetic label and less likely to view government or institutional involvement in health assessment as a positive development.

It is important that while the early Tay-Sachs programs were not extensively taken up by the entire Jewish-American community, many of their innovative features were subsequently found to be of great value. The same approach was used 25 years later to organize a study of heritable breast cancer in Ashkenazi Jews. Some of the earliest Tay-Sachs programs were organized at synagogues. In advance of implementing the screening programs, a series of productive meetings and discussion forums were held between physicians, ethicists, rabbis, and other members of the particular Jewish religious communities. As a result of these meetings, physicians and public health workers developed programs that focused on young Ashkenazi Jewish married couples who were considering having a child; other programs expanded this target group to include all unmarried members of the Ashkenazi Jewish community who were 18 years old or older.

Another positive feature of the early synagogue-based Tay-Sachs screening programs is that religious leaders and community volunteers worked side by side with physicians and genetics counselors to provide education at the screening site as well as to answer any questions the participants might have. Informed consents were

routinely obtained and several steps were taken to ensure confidentiality. Those who tested positive for the carrier state were telephoned. Genetic counseling for individuals positive for Tay-Sachs was then offered, especially to those couples who both tested positive for the carrier state. In general, the woman in such couples underwent prenatal diagnostic testing of amniotic fluid when she became pregnant. The majority of those couples who were discovered to be carrying a fetus afflicted with Tay-Sachs disease elected to terminate the pregnancy.""

This focus on religious institutions and communities was not entirely successful. Not all Jews were members of a synagogue and different areas in the United States and Canada embraced these programs at markedly different rates. For example, in Toronto, the Jewish community actively joined forces with the medical and public health communities to establish programs in the early 1970s, while in Montreal, the Jewish community did not. One impetus for the design of a well-known study was the lack of interest in Tay-Sachs screening among the Montreal Jewish community, leading the investigators to develop a study that "captured" Jewish high school students.

There are, of course, many different sectors of the Jewish-American community, divided along lines of religiosity (e.g., the Orthodox, Conservative, Reform movements, as well as non-practicing or secular Jews), place of geographic origin, economic status, and a number of other social factors that were recognized by the partnership of religious and community leaders and the medical establishment. One effort to address these differences was the Chevra Dor Yeshorim Program of New York City, designed to accommodate the cultural customs and religious beliefs of ultra-Orthodox Jews. Developed in partnership with members of the Orthodox-Hassidic Jewish community, which has a high risk of Tay-Sachs disease and strong opposition to abortion and contraception, this program relies on this community's practice of arranged marriages. When a Hassidic Jewish woman reaches 18 years of age or a man 20, the subject undergoes a blood test for Tay-Sachs disease. The laboratory handling the test assigns a code number to the sample and it is tested anonymously. The results are listed and stored by code number indefinitely. The subject is given only the code number but not the actual results of the test. At the time of a planned marriage, the shadchen, or matchmaker, is given the code numbers of the prospective bride and groom and presents them to the laboratory registry. If both partners are positive for the carrier state, the matchmaker is told that the match is not a good one and another match is arranged. If a couple does not use a matchmaker, they, too, may inquire of their status from the registry and make their decisions accordingly.* A central aim of this plan is to keep the effects of genetic stigmatization to a minimum. Couples screening programs have been applied to cystic fibrosis (CF) in Scotland and England, and in Maine. The CF programs are similar to Chevra Dor Yeshorim in that only couples who were both positive for the trait are informed of the result; if only one partner is a carrier, s/he is not informed. The difference is that married couples are tested for CF.' This program has since been applied to Orthodox Jewish communities elsewhere in the United States, Canada, Europe, and Israel.'

As large populations were tested, problems surfaced concerning the reliability and validity of the available Tay-Sachs screening tools. For example, the earliest Tay-Sachs screening tests were plagued with an unacceptable rate of "false positives." Women concurrently using oral birth control pills were 50 percent or more likely to have a false-positive carrier test result. Other medications were discovered to be the cause of a false-negative carrier result. Fortunately, several research consortiums that were devoted to the prevention of Tay-Sachs disease conducted follow-up studies to identify and correct such problems in test validity.

The critically important, and potentially overlooked, lesson is that any genetic screening program must provide unrelenting vigilance in the implementation of such tests on large numbers of people, in addition to the careful

surveillance of test development.

Since 1971, screening programs directed at the Ashkenazi Jewish population in the United States and Canada have led to a 90 percent reduction in Tay-Sachs disease. The Tay-Sachs screening programs are often recalled as a success in the blending of science, bioethics, and disease prevention. At the same time, several follow-up studies have documented that, although genetic counseling alleviated some of the anxieties experienced by the heterozygous, phenotypically normal Tay-Sachs carriers, there was evidence of residual unease among many of them simply at potentially being labeled a carrier.""

PRENATAL SCREENS FOR DOWN SYNDROME AND NEURAL TUBE DEFECTS:

APPLYING WHAT WE HAVE LEARNED TO THE DEVELOPMENT OF

NEW GENETIC SCREENING TESTS

Over the past three decades, a number of technologies have been developed giving physicians better means of gaining information about genetic and physical aspects of the developing fetus. A striking example is Brock and Sutcliffe's 1972 description of the association of elevated levels of amniotic fluid alpha-fetoprotein in the antenatal diagnosis of neural tube defects such as anencephaly and spina bifida. Subsequent studies found an association between elevated maternal serum alpha-fetoprotein (MSAFP) levels and the incidence of neural tube defects.

The transfer of this technology across the Atlantic Ocean might be best characterized as stormy. Early on, several enterprising American biotechnology firms vied to secure the FDA license for the manufacture of AFP screening kits. Initially such distinguished medical bodies as the American College of Obstetrics and Gynecology and the American Academy of Pediatrics, however, expressed serious concerns about the marketing of such a diagnostic tool, given that practicing obstetricians at that time did not fully understand the limitations of the test and the need for follow-up testing. Others wondered if the fragmented, almost cottage-industry American health care system of the early 1980s might create obstructions to conducting a safe and smooth testing program in comparison to the nationalized health care system that existed concurrently in Great Britain.

Politics, too, had a significant effect on these programs, in that the FDA suggested restrictions to the use of AFP kits in 1980 that would have increased the likelihood of a well-run genetics screening program. They were ignored by the Reagan Administration. In spite of the tremendous controversy generated in the United States, the Food and Drug Administration gave pre-market approval to manufacturers of AFP kits in 1983. Soon thereafter, it became fairly routine for physicians to obtain serum alpha-fetoprotein levels of pregnant women in the United States as a screening test for these birth defects.

During the mid-1980s, concurrent work by several geneticists noted the association of low maternal serum alpha-fetoprotein levels with chromosomal abnormalities such as Down syndrome (Trisomy 21) and Trisomy 18.› The risk of a baby being born with Down syndrome increases with maternal age, and this association is noted in mothers of all ages. For example, while the overall incidence rate for Down syndrome is 1/600-800 live births, the risk of Down syndrome increases with maternal age is markedly more common in a child born to a woman over 35 years of age (1/365), and the rate of incidence increases with each year of age. (e.g., 24-year-old women have an incidence of only 1/1,300, while 40-year-old women have a 1/110 incidence and 45-year-old women have a 1/41 incidence). It is important to note that despite the much higher rate of Down syndrome in the offspring of older pregnant women, the majority of Down syndrome infants are born to younger women, simply because most pregnancies occur in women under 35 years of age. The AFP tests offered a safe,

inexpensive (when compared to amniocentesis and karyotyping) means of screening lower-risk younger women who parented the largest number of affected infants. The tests' use has broadened over the past decade and they are routinely offered to those pregnant women who have access to prenatal care in the United States.

The maternal serum alpha-fetoprotein assay is a first-step screening test. It does not diagnose disease; rather it identifies most of those who are deemed to be at increased risk and who require further testing for a definitive diagnosis. A particular benefit to this screening test is that it is a relatively low risk and inexpensive medical procedure. A blood sample is taken from the mother at 15 to 20 weeks of gestation. The recently developed Down syndrome "triple marker" screen of MSAFP, maternal serum unesterified estriol, and maternal serum human chorionic gonadotropin increases the detection rate from 20 percent for MSAFP alone to 60 percent. Elevated or decreased levels are then followed by more definitive, and costly, ultrasonic examination and amniocentesis.

It is, therefore, essential for both the health provider and the patient to understand that an elevated AFP is not diagnostic for neural tube defects; nor is a low AFP diagnostic of Down syndrome. These aberrant levels, in fact, may be associated with a large number of disorders or may not be associated with any fetal abnormality at all. There also exists a high association of falsely elevated AFP levels due to misdating of the pregnancy, multiple births, errors in reporting or determining race, diabetes mellitus, errors in calculating body weight, laboratory errors and physician misinterpretation.

Subsequent studies on the interactions between female patient and male health care provider suggest that gender differences have an impact on the patient's own ethical decision making. Wertz has documented how health care providers and patients have significantly different perceptions on the assessment of genetic risks. Press and Browner analyzed the decisions of an ethnically and socioeconomically diverse group of women to refuse or accept a prenatal diagnostic test. The factors that determined the decisionmaking process of these women in the early 1990s was neither ethnic nor social class related; instead, the determining factor was how the women were informed about the tests. Press and Browner hypothesized that the women and health care professionals involved in these clinical interactions create a "collective fiction" that "situate[s] the testing within the domain of routine prenatal care and denie[s] its central connection to selective abortion and its eugenic implications." As a result of these and similar studies of patients' experience undergoing genetic screening tests, we are beginning to appreciate the great potential that exists for patient (and physician) misunderstanding, conflicts over ethnic and gender issues, and anxiety about the test results.”

Interestingly, despite close scrutiny by the scientific genetics community, the AFP, estriol, and chorionic gonadotropin ("triple") screens for Down syndrome have not been fully evaluated or regulated by the Food and Drug Administration. A close follow-up of these screens and definitive policies for their use is an important aspect of this program that has not been fully addressed.

CONCLUSIONS

This brief historical review of the sickle cell, Tay-Sachs, neural tube defects and Down syndrome screening programs presents many lessons that can be learned from the past:

- Sensitivity to the needs of the groups screened and the inclusion of those groups in the planning of screening programs can frame the diagnosis and understanding of genetic disease with respect to issues of race, ethnicity, and gender;

• Patients, physicians, and genetic counselors must understand what these tests actually predict or diagnose in order to ensure that patients make fully informed, autonomous decisions about the test results;

• Unrelenting vigilance is necessary on the validity of tests and the reliability of the laboratories providing them, both as the tests are developed and as they are used on large numbers of people;

• It is important to consider how these test results may effect other family members;

• Confidentiality of the information discovered is vital;

• The impact of a genetic diagnosis on the patient's health or life insurance status must be carefully considered; and

• An ethical dilemma is posed by disease avoidance using pregnancy termination.

This last dilemma exemplifies the deeper question of just what one is going to do with the results of these screens. No definitive treatments yet exist for Down syndrome, neural tube defects, Tay-Sachs disease and many other prenatally detectable genetic conditions. The principal means of disease prevention for these disorders is pregnancy termination.*

There are prospective parents for whom abortion is not an acceptable alternative. Early 20th century eugenicists might call such a selection process negative eugenics**; late 20th century fundamentalist Christians would deem such an option as murder of an unborn child. Similarly, ultra-orthodox Jews and observant Roman Catholics do not accept abortion as an option. Indeed, the health care provider's own views on abortion may have an impact on the information and options provided to the parents of an affected fetus. Furthermore, anti-abortion (pro-life) activists, and their pro-choice or abortion rights counterparts, have become increasingly focused on genetic screening programs since the mid-1980s, which brings a high-stakes political element to the clinical arena. All of these political spins will have to be taken into account as policymakers continue to plan and develop prenatal screening programs for serious diseases that at the present have no treatment.

The benefits and the liabilities of these nascent technologies and medical breakthroughs are of concern to all of society, but are of particularly critical importance to those involved in genetic research, medical practice, and public health policy. New developments will bring both old and new dilemmas to the surface so that some of these issues may become irrelevant, depending on how technology, society, and culture evolve. Other issues, particularly race, ethnicity, and gender, appear to return perennially to genetic testing programs.

If history teaches us anything about genetic screening, and more broadly, about the ethical use of biotechnology, it is that careful discussion and planning goes a long way in ameliorating many of their associated difficult issues. We must address such issues before inappropriate uses or applications become socially embedded in our medical practices and must be open to the recognition of dilemmas that become apparent after the implementation of a genetic screening program.

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