SICKLE CELL SCREENING POLICIES AS PORTENT: HOW WILL THE HUMAN GENOME PROJECT AFFECT PUBLIC SECTOR GENETIC SERVICES?

David D. Phoenix, DrPH, Sherrill M. Lybrook, MS, Ralph W. Trottier, PhD, JD,
Faye Cobb Hodgin, PhD, JD, and Lee A. Crandall, PhD
Clemson, South Carolina; Atlanta, Georgia; and Champaign, Illinois

The Human Genome Project holds much promise for providing dramatic improvements in our understanding of and means to diagnose and treat many diseases. As this enormously important endeavor proceeds, research on ethical, legal, and social implications of this new science is being conducted to forecast problems and recommend policy option solutions to avoid what might otherwise become adverse consequences. Sickle cell screening is an example of a technology that was introduced in a manner that raised poignant issues. On the basis of sickle cell issues, we examined policy issues likely to occur as new genetic technologies are incorporated into medical practice. Discussion and development of a national consensus on the appropriate content and just delivery of public sector genetic services is vital; otherwise, the impact of Human Genome Project-derived technology may result in misadventures that amplify problems currently evident in newborn screening programs. New DNA-based diagnostic technologies and therapies will soon enter the stream of commerce. The recommendations offered here, while based on examination of sickle cell disease policies, are intended to address both current inequities as well as potential future issues related to stigmatization and distributive justice. (*J Natl Med Assoc.* 1995;87:807-812.)

Key words • sickle cell anemia • sickle cell screening • Human Genome Project

This article addresses issues identified during the course of research on ethical, legal, and social implications (ELSI) of the Human Genome Project (HGP).[1,2] The term sickle cell (abbreviated "SC") in this article does not imply a specific form of hemobgobin. Sickle cell anemia portends issues that must be faced as the HGP progresses. Cost-effective tests are available to determine carrier state and affected individuals. While there is no cure for Sickle cell disease, medical intervention and treatment reduce morbidity and mortality.[3] Technology now provides for prenatal and newborn SC detection and also the potential for preimplantation detection.[4] Sickle cell disease, found in a wide range of ethnic groups, is most prevalent in certain minority populations.[5] Newborn screening programs in some states (eg, Georgia) target "susceptible" ethnic groups (OCGA. §31-12-7[a]; Rules of Department of Human Resources (DHR)/Public Health Chapter 290-5-24 [290-5-24-.03]). Sickle cell disease is a model for potential difficulties that may be encountered as the HGP fosters new disease detection capabilities.

The HGP may serve as the catalyst for substantial changes in newborn screening and other public sector

From the Department of Health Sciences, College of Nursing, Clemson University, Clemson, South Carolina; the Department of Pharmacology and Toxicology, Morehouse School of Medicine, Atlanta, Georgia; and the Department of Community Health, University of Illinois, Champaign, Illinois. This research was supported by funds provided through a cooperative agreement between the Human Genome Project ELSI programs of the US Department of Energy and the National Institutes of Health, Grant #DE–FG02–92ER61396, administered by the US Department of Energy, Office of Energy Research and by funds received from the Morehouse School of Medicine, Research Centers in Minority Institutions Grant #RR03034. Requests for reprints should be addressed to Dr Ralph W. Trottier, Professor, Dept of Pharmacology and Toxicology, Morehouse School of Medicine, 720 Westview Dr, SW, Atlanta, GA 30310.

genetic services programs.[6-8] Human Genome Project science (sequencing DNA and mapping genes on chromosomes) is well ahead of its initial 5-year plan, and the discovery and use of molecular diagnostics is expected to proceed at breakneck speed.[9] These developments undoubtedly will challenge existing mechanisms of service delivery to the public and raise the need to prepare for a broad public impact.[10]

STUDY DESIGN

National newborn screening programs were considered to be first-line public sector genetic services. Sickle cell screening was of particular interest because of the significant ELSI questions it raises from both historical and future perspectives. Sickle cell screening also raises unsettled issues from a medical and ethical viewpoint. Sickle cell is the only condition in newborn screening programs in which the screening process identifies carrier state individuals as well as those affected by the disease. The structure and processes of the Georgia sickle cell newborn screening program were studied in detail. In-depth interviews with acknowledged authorities and practicing professionals and site visits were conducted at an urban SC center, the Sickle Cell Foundation of Georgia and two SC outreach clinics. The culturally diverse population, large urban areas separated by considerable distances, and the many rural counties of Georgia provide an opportune setting to examine a broad spectrum of issues pertinent to the public impact of the HGP. Georgia has a significant (27%) African-American population, a growing rural population of other SC-susceptible ethnic groups, and regional variability in the distribution of minority populations throughout the state.

FINDINGS AND DISCUSSION

Including the 50 states plus the District of Columbia, Puerto Rico, and the Virgin Islands, 34 of 53 sovereign entities screen all newborns for hemoglobinopathies (SC included). Nine use some form of targeted screening, and 10 do not screen for hemoglobinopathies.[11] In six of the nine states in which SC screening is targeted to particular races/ethnic groups or is regional in operation, the program is voluntary. In comparison, screening is voluntary in only 7 of the newborn screening programs among states screening universally for SC.[11] It has been reported that newborn screening programs have evolved as much or more from a politically based process than from a perceived medical necessity.[7] The "politics" of SC screening are implicitly, if not expressly, included in the process of newborn screening.[11] However, analysis of national NBS programs along the spectrum of "targeted/voluntary" to "universal/mandatory" reveals no apparent patterns, political or otherwise.

For example, Vermont, reporting a 0.5% African-American live birth population rate (a total of 41 births), and New Hampshire (1% African-American live births, [173 births]) have targeted voluntary SC newborn screening programs; conversely, Wyoming, a state with a similarly low minority population base (1.5% African-American live births [99 births]), has a universal mandatory SC newborn screening program.[11,12] Similarly, striking contrasts are noted in other regions of the continental United States. Nebraska (6.4% African-American live births, [1546 births]) does not have a SC newborn screening program while Iowa (3.4% African-American live births, [1335 births]) has a universal mandatory SC newborn screening program.[11,12] Based on these examples, there does not appear to be a correlation of program existence or type along lines of African-American birth rates, geographic size, or region. In those states in which SC screening is currently targeted, there appears to be a greater likelihood that the program is voluntary rather than mandatory; however, there appear to be no regional or other distinguishing characteristics that differentiate SC screening voluntary programs from mandatory ones. Of the potential newborn screening tests found in the battery of generally tested conditions, SC is the only screen that is treated disparately with regard to ethnic/racial targeting.

To gain a better understanding of programmatic operation in detail, we examined the SC newborn screening program in Georgia. This program is unique in that its targeted SC screening component has both voluntary and mandatory characteristics. This seemingly oxymoronic description and the operational problems described below result from the language of the newborn screening statute (OCGA §31-12-7[a]) directing the Georgia DHR to establish a program to test all newborns who are "susceptible or likely to have phenylketonuria, sickle cell anemia, or sickle cell trait ——." Although phenylketonuria appears in this section of the statute along with SC, it appears as well in an earlier section under categories of other conditions for which all newborns shall be screened (OCGA §31-12-6[a],[c]). The statute gives broad authority to DHR to configure a plan for phenylketonuria and SC newborn screening. The plan configured by the DHR is described in Rules of the DHR—Public Health, Chapter 290-5-24 (March 2, 1983), and states in part .03(c)—Sickle Cell Testing, Amended: "Infants with either or both parents of African, Arabian, Greek, Maltese, Portuguese, Puerto Rican, Sardinian, Sicilian, South and Central American, Southern Asian, and Spanish origin which is to be determined by information provided on the informed consent form."

The forms examined reflect the statutory language regarding the particular ethnic groups regarded as "susceptible" and targeted for screening. The forms provide for "consent" to testing or "objection" based on "religious reasons." Some forms contained a separate section on metabolic disorder screening, enumerating the conditions to be tested for and allowing for "consent" or "objection" as described for SC. Confusion arises as to what is voluntary and what is mandatory. On the one hand, the law clearly provides for mandatory testing of all newborns for particular conditions and susceptible newborns in the cases of phenylketonuria and SC; on the other hand, the information on the forms implies that consent is required to proceed with screening. The voluntary aspect of the DHR regulation is supposedly self-identification of ethnic/racial origin by the mother. It is not clear whether hospital staff attempt to determine or question the ethnicity of either the mother or father on admission to labor and delivery. Some hospitals treat the entire newborn screening scheme as "voluntary" and fail to screen if consent is not provided by the mother (Henson M.A. unpublished data.)

It is noteworthy that the DHR did not design a screen along the lines of susceptibility for phenylketonuria despite the fact that it was empowered by statute to do so and that phenylketonuria is rare in some of the ethnic groups targeted in the SC scheme.[13] According to a legal analysis, the DHR could require SC screening of all newborns (presumably determining that all are susceptible to SC) or restrict screening to susceptible newborns where clearly defined and articulable guidelines are provided (Op Att'y Gen No. 81-40, May 20, 1981). This opinion also provides an answer to the query as to whether the attending physician shall decide who is "susceptible" to SC anemia or SC trait in addition to any information provided by the mother. The opinion concludes that such an analysis by medical experts is appropriate provided, however, that the DHR clearly articulates guidelines to assist physicians in making the susceptibility determination. Current DHR rules provide no such guidelines. Indeed, attempting to articulate criteria to determine SC susceptibility would be an ominous task considering the shifting demographic patterns of SC and the fact that approximately 10% of patients with sickling disorders identify themselves as something other than black.[14] Courts have been reluctant to impose a broad duty to detect susceptibility to a genetic condition where information on heritage was neither evident through profile characteristics nor revealed by the patient (*Munro v Regents of the University of California*, 215 Cal App 3d 977, 263 Cal Rptr 878 [1989]).

Our investigation of SC programmatic operation in Georgia also examined distribution and availability of services. The division of public health has established nine SC clinics located in municipalities south of the comprehensive sickle cell center in Atlanta. These municipalities are typically county seats in regions with high African-American population bases (35% to 50%).[15] The program provides service to areas in the state having the greatest distribution of African-Americans. In more northern areas of the state typically having a sparse African-American population and distant from the Atlanta or Augusta (tertiary care center locations), SC patients are seen in organized public sector genetics outreach clinics. These regions are experiencing a growing Hispanic population, an ethnic group included in the newborn screening targeted scheme. This discussion is not meant to imply that SC services are readily available and convenient to all in need. Interview informants described a variety of domestic and transportation hardships that act as barriers to access and service availability. Problems notwithstanding, the overall plan appears to address equitable and just principles of service delivery considering its currently targeted focus and given the resource construct within which it operates.

Two peculiarities were noted in the newborn screening data reported by Georgia as well as by the Council of Regional Networks for Genetic Services (CORN). The first is that hemoglobinopathy is the only category of newborn screening broken down along lines of race. The second, by virtue of the nature of the laboratory test, SC is currently the only newborn screening test in which trait carriers are incidentally identified. The issue of carrier identification in the newborn screening paradigm has drawn much criticism.[16] Current schools of thought about genetic trait testing vary. One opposes autosomal recessive carrier status detection through newborn screening to be used for the purpose of assisting parents to learn of their own carrier status because trait carrier detection is of no clear, direct benefit to the newborn, and the information may result in harmful stigmatization of the newborn and the family. The same report, however, supports carrier testing through other avenues such as voluntary testing through preconceptional or prenatal services since not learning about carrier status through newborn screening puts the parent(s) at the disadvantage of not being able to make an informed decision on whether to be tested. The issue of what happens to the information if it is not revealed to the parent(s) is unsettled. Although it may not be of immediate benefit to the newborn and given that it may result in discrimination or stigmatization in some manner, it is arguable that carrier status knowledge may be nonetheless important to the person at some later time in

life. The broad questions would be who stores the information, how is it stored and at what point should it be made available to the owner? Proponents of disclosure to the parent(s) rationalize their position on the basis that the information could be useful to them in making future reproductive decisions. From this perspective, the parent(s) would be afforded the opportunity to choose whether to be tested, and disclosing the information would fulfill principles of beneficence and respect for autonomy. Recommendations have been made that all parents of newborn screening SC (and other variant hemoglobinopathy) carriers should be contacted for individual counseling, education, and extended family testing.[17]

The translation of genetic information into reproductive decisions and other family dynamics is the subject of an ongoing investigation.[18] Researchers in that study have found that although African-Americans are more likely to have been tested for SC carrier status, they are more reluctant to integrate this information into reproductive decision making than are carriers of cystic fibrosis. Whether this difference is attributable to the potential disease nature of cystic fibrosis compared with SC or to cultural value differences remains to be resolved. Differences in racial distribution patterns commonly used in descriptions of autosomal recessive conditions, may become less important over time. For example, Tay-Sachs disease is now reported to occur with greater frequency in non-Jewish newborns.[16]

As HGP research progresses, inexpensive technologies that precisely detect disease onset, development, or causation will precede the development of therapies. DNA-based diagnostic technology may soon replace the current methods used in newborn screening laboratories. A current study demonstrates the advantages of molecular genetic testing in reducing the time (by 50%) required to confirm hemoglobinopathy diagnoses made through conventional (blood spot) newborn screening.[19] Other applications are expected from HGP science.

CONCLUSIONS AND RECOMMENDATIONS

Undeniably, cultural sensitivity is of considerable importance in the delivery of genetic services in the public sector as well as in the private sector. Cultural sensitivity involves not only issues of race but also issues of stigmatization based on gender discrimination in various ethnic groups.[20,21] Cognizance of and respect for religious beliefs and family member roles in diverse cultures and cultural traditions are necessary to address the needs of cultural appropriateness. Given that state newborn screening programs, whether voluntary or mandatory, are already established throughout the nation, it is likely that this as well as other public sector genetic services (eg, genetic clinic outreach programs) will become increasingly important aspects of public health.[9,22,23] This is especially so as new DNA-based technologies become available and cost effective and as public health services are encouraged to assume new roles in health-care reform measures.[24] To address issues of cultural sensitivity, we recommend that each state review its newborn screening legislation to ensure that the statutes are accurate and timely with regard to the meaning of medical terminology. Every effort should be made to change or eliminate language that is stigmatizing or implies discriminatory treatment.

Targeted programs for SC screening, voluntary or mandatory, seem medically, ethically, and legally untenable. A study reporting that targeted screening was found to miss 20% of Afircan-American newborns is evidence that the system may adversely impact the persons expressly intended to benefit from it.[25] A state may be held liable for failure to diagnose a condition through its newborn screening program (*Marcel v Louisiana State Department of Health and Human Resources*, 492 So 2d 103 [La Ct App 1986]). This picture becomes more complex in an era of increasing acceptance of wrongful birth as a cause of action in tort (*Reed v Campagnolo*, 630 A 2d 1145 [Md 1993]) as well as recognition of the legal status of a fetus as a person (*Gulf Life Ins Co v Brown*, 181 Ga App 72, 351 S E 2d 267 [1986]). We support the trend toward universal screening for SC.

Issues of the cost effectiveness of universal screening for SC (or other conditions in NBS profiles) may be addressed through the formation of state screening cooperatives.[11] Although cost effectiveness is certain to continue to be a driving factor in the distribution of American health care, the 25-year nationwide SC screening experience undoubtedly would reveal that individual benefits and public good of early SC detection outweigh cost-effectiveness considerations. A study needs to be conducted to determine the feasibility of configuring cooperatives along lines of existing or rearranged CORN regional genetics groups. In light of new DNA-based technologies likely to arise soon from HGP research and the fact that "high-risk" or "low-risk" populations are not distributed homogeneously either among or within states, consideration of unified cooperatives forecasts a logical direction for newborn screening programs. Cooperatives also may provide cohesive forums to address whether newborn screening should be voluntary or mandatory. Mandatory newborn screening programs represent systems of legislated medical practice. As noted above, most newborn screening programs are legislatively mandatory.

One study poses an interesting challenge to compulsory newborn screening programs and concludes that such programs have not achieved any public benefit superior to that demonstrated by a voluntary program.[26]

Whether any form of genetics belongs at all in the public health domain is an issue in controversy. The recently released Institute of Medicine report argues that genetics does not fit the traditional public health preventive medicine paradigm.[16] This conclusion, however, was narrowly drawn along lines of the role of public health in addressing environmental issues and contagion. Other investigators oppose the Institute of Medicine view, rationalizing the role of genetics in the context of a much broader public health impact.[27] Our study revealed that the public sector is the sole source of genetic medical services for large segments (particularly rural areas) of the populations of Georgia and Florida. We suspect this situation is generalizable to other states.

Issues analogous to those raised by SC are bound to be as salient to other conditions for which DNA-based diagnostics will provide avenues to identify persons affected prior to availability of effective prevention or intervention. In addition, it seems that carrier status identification will be incidental to detecting homozygous states. Regardless of whether newborn screening remains a state-based effort or becomes regionalized through the formation of state cooperatives, advisory boards should be formally appointed and empowered to make recommendations regarding genetic medical services in public sector programs. An example is found in the current Florida NBS statute (FSA §383.14[5]). Moreover, these boards should include of a person with formal training in medical ethics as well as representation of ethnic minorities. Carrier status information, whether obtained through either inadvertent or purposeful design, should not be revealed to the parent or to the adult to which it pertains without first obtaining full informed consent regarding its meaning. In the consent process, all medical and social risks and benefits associated with revealing and knowing that information must be disclosed. Policy recommendations regarding a broad form of consent for genetic screening recently have been made by others.[28] The marketing of DNA diagnostic technologies is anticipated to be followed by burgeoning gene therapy advances. How rapidly the latter advances will be made is, at this time, speculative, but recent progress in gene therapy for SC and Duchenne muscular dystrophy forecasts a likely escalating trend.[29,30] Research to predict SC disease severity through identification of DNA markers is also in progress.[4] The biotechnology industry stands ready to compete for funds from the US Department of Commerce's advanced technology program to develop applications based on HGP research. Plans for a state-of-the-art miniaturized DNA diagnostic device have been described (US Dept of Commerce, unpublished data, 1994).These advances are taking place during a time in which little, if any, cohesive, organized thought and attention is being paid to the direction and role of new genetics in the public sector. Our research reveals that intrastate variability in genetic services raises the same issues of distributive justice as does interstate variability of other medical services. There are more than 3000 state counties nationwide, each with the potential of functioning with great independence with respect to public sector health services. Issues of justice in health care arise where there is an apparent failure of a system to provide for services of particular importance to politically and economically disadvantaged minorities or where there is failure to make available services to the benefit of the public at large without regard to racial or ethnic status. A national assessment of issues pertaining to public sector genetics is of great importance and has been neglected thus far.

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