Introduction: New Technologies for Genetic and Newborn Screening

MARGRETTA REED SEASHORE, M.D., AND CATHERINE WALSH-VOCKLEY, M.S.

Department of Human Genetics, Yale University School of Medicine, New Haven, Connecticut

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Screening newborn infants for inherited disorders has been effective in preventing mental retardation, growth failure, and death from several metabolic disorders for more than two decades. Technical advances have provided more screening tools for both genetic and non-genetic conditions, and in the coming decades these techniques will be used not only to screen newborns but to assess genetic risks in entire populations. The financial, legal, and ethical issues which these activities raise must influence the development of public policies in order to reap the benefits promised. The conference published here was designed to address these issues for health care practitioners, health policy planners, and public health professionals.

"New Technologies for Genetic and Newborn Screening: A Medical, Legal, and Ethical Update," a symposium hosted by Yale University School of Medicine on April 23, 1990, in New Haven, was designed to address four areas of importance in the development and use of newborn and population screening for genetic disorders:

- Examples of new technologies, especially molecular genetic tools
- Implementation of new technology, especially laboratory, educational, and counseling functions
- Applications to non-genetic diseases such as infectious diseases, especially public policy and ethical considerations
- Medical-legal, ethical, and financial issues, including legal mandating of screening, confidentiality of results, responsibility for follow-up, and stigmatization of those screened

The papers in this symposium include two talks given at the beginning: the keynote address, "Genetic Screening for the Next Decade: Application of Present and New Technologies," by Edward McCabe, M.D., Ph.D., Baylor College of Medicine, and "Legal Aspects of Genetic Information," by Lori Andrews, J.D., American Bar Association. Rodney Hoff, D.Sc., New England Newborn Screening Program, discussed "Newborn Screening for Non-Genetic Disease." This discussion has been published elsewhere [6] and is reviewed briefly in this paper.

Two panel discussions, "Implementation of New Technologies," chaired by Margretta R. Seashore, M.D., Yale University School of Medicine, and "Ethical, Legal, and Financial Issues in Genetic Screening," chaired by Maurice J. Mahoney, M.D., Yale University School of Medicine, formed the rest of the symposium. Panel

Abbreviations: AIDS: acquired immunodeficiency syndrome  ELISA: enzyme-linked immunosorbent assay  HIV: human immunodeficiency virus  NERGG: New England Regional Genetics Group  PCR: polymerase chain reaction  PKU: phenylketonuria

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members included Edward McCabe, M.D., Ph.D., Baylor College of Medicine; Edwin Naylor, M.D., University of Pittsburgh; Harvey Levy, M.D., Harvard Medical School; Catherine Walsh-Vockley, M.S., Yale University School of Medicine; Philip Reilly, M.D., J.D., Eunice K. Shriver Center; Paul Billings, M.D., Harvard University; and Robert Pokorski, M.D., Lincoln National Life Insurance Company. Questions addressed to the panelists from the audience follow the summaries of each panel discussion.

Nearly three decades have passed since the introduction of newborn screening for inborn errors of metabolism, and the developments have been recently reviewed [1]. These programs were initially undertaken to detect infants affected with phenylketonuria (PKU) in order to treat them and thus prevent the mental retardation associated with PKU. Phenylketonuria had been recognized as an inherited cause of mental retardation since Folling's original description in 1930, but it was not until Woolf, Hudson, Bickel, and others applied a phenylalanine-restricted diet to treat these infants that the need for identifying affected infants before they became mentally damaged became critical. The development in 1962 of a bacterial inhibition assay which would measure the concentration of phenylalanine in the blood of newborn infants paved the way for early treatment of these infants. The method was simple and employed a small amount of blood soaked into filter paper and mailed to a central laboratory. Screening programs based on this technology now exist in laboratories around the world. The programs have led to improved understanding of the natural history, treatment, and genetics of important causes of infant morbidity and mortality and mental retardation. Tests for an increasing number of disorders have been applied. Most of these methods involve measurement of an excess or deficiency of a metabolite, a protein, or an enzyme.

Galactosemia, a disorder due to deficient metabolism of galactose (a component of the sugar lactose present in milk) can be identified by measuring galactose in red blood cells or by measuring the relevant enzymes, galactose-1-phosphate uridyl transferase and galactokinase, in whole blood. Hypothyroidism, a condition due to deficiency of thyroid hormone (and not usually inherited) can be detected by measuring thyroid hormone in the blood. Both of these are disorders for which newborn screening has been applied, using the Guthrie filter paper cards, in most states throughout the United States as well as in Canada, Europe, and Japan. The effect on mortality from galactosemia has been dramatic, although there is still much to be learned about optimal treatment to prevent learning disability. Newborn screening for congenital hypothyroidism has been highly successful in preventing long-term mental deficiency as well as retardation of growth and development.

Although the technology used in newborn screening for metabolic disorders has been developed and refined for the last 30 years, the principles and goals embodied in many of the basic ideas remain unchanged [2]. The major goal of newborn screening programs is to prevent serious morbidity or death from a treatable disorder by identifying affected infants prior to the development of symptoms. This goal has been expanded to include genetic counseling for families of affected infants. The development of new technology for newborn screening must be in harmony with these well-accepted goals.

A second application of genetic screening is heterozygote screening, designed to identify individuals or couples at risk for having children with a serious genetic disorder. Tay-Sachs disease was the first inherited condition for which wide-scale
population screening for heterozygosity was performed. The identification of the biochemical defect in this disorder and the demonstration [3] of half normal activity of the defective enzyme, hexosaminidase A, in the serum of obligate carriers of the Tay-Sachs disease gene made screening theoretically possible. The technology which made enzyme analysis both automated and accurate turned this theoretical possibility into a reality. Tay-Sachs disease was an excellent model for population screening for at least three reasons. The disorder is severe, it results in neurodegeneration leading to death, and it is untreatable. The population at highest risk is well defined: the Ashkenazic Jewish population. An intervention, accurate prenatal diagnosis of affected fetuses, is available. Experience around the world led to the development of principles for heterozygote screening that can be applied to other disorders [4]. Advance planning, careful education of the target population, precise definition of the population to be screened, and strict attention to technical matters are absolute essentials in a heterozygote screening program. Not the least of the effort is spent in education of the medical and public health professionals who will be asked to support programs and to help in the education and follow-up of individuals tested. The psychosocial risks of stigmatization and loss of self-esteem cannot be ignored. Despite these caveats, the Tay-Sachs screening programs around the world have been highly successful, and the incidence of Tay-Sachs disease in the Ashkenazic population has decreased dramatically [5]. As the technology has been developed, screening for heterozygosity for other inherited disorders such as sickle-cell anemia and thalassemia has become possible, and screening populations for the common cystic fibrosis mutations is nearly available. With the establishment of screening programs for these disorders, the need to develop educational and counseling methods to accompany the screening tests has become ever more obvious.

New technologies have created new opportunities to identify those at risk for the development of serious genetic disorders. These opportunities include the chance to identify those at risk for a broad range of disorders and to offer intervention, including treatment, prenatal diagnosis, and genetic counseling. In addition, physicians, scientists, and others can learn more about the specific inherited conditions and about the effect of genetic screening. Technical, ethical, and legal questions raised by these developments are the subject of the papers by McCabe, Naylor, and Andrews in this symposium.

Some of the techniques developed for screening in genetic screening programs may be applicable to environmental screening—for example, newborn screening for toxoplasmosis and human immunodeficiency virus infection [6]. The goals of screening for these non-genetic disorders are similar to the goals of screening for genetic conditions; that is, intervention and counseling. Toxoplasmosis is an infectious disease which leads to chorioretinitis and central nervous system damage when it is contracted during fetal life. Transplacental transmission occurs in about 40 percent of infants whose mothers have active disease. Many of these congenital infections are clinically inapparent. Treatment with antimicrobial agents slows the reproduction of the organism and ameliorates the disease in the infant. Hoff has reported [6] that screening newborn blood samples from Guthrie cards using enzyme-linked immunosorbent assay (ELISA) is effective in identifying infants who have antibodies to this organism and who thus need further testing. Perinatal acquired immunodeficiency syndrome (AIDS) due to human immunodeficiency virus (HIV) infection is becoming a serious problem; as many as 30 percent of infants born to seropositive
mothers may become infected. Because of problems of interpretation of serological studies for HIV infection, methods using the polymerase chain reaction (PCR) to identify the presence of HIV proviral DNA in the blood are being developed. The extension of this technology to screening of the newborn infant is just beginning [6]. Although satisfactory treatment for AIDS is not yet available, the screening procedures would facilitate both diagnosis and counseling for reproductive planning.

These new technologies may, however, cause serious repercussions throughout the health care system. They may contribute to the increasing cost of medical care before the influence of their role in disease prevention is felt. Billings and Pokorski examine the problems that increasing numbers of people at known risks create for insurance companies, health maintenance organizations, and other third-party payers. Billings and Reilly point out that important privacy concerns must be addressed as such persons are identified, and Pokorski and Reilly address the possible uses and misuses of this information by others—for example, insurance companies. Legal issues, including the need to set standards of care and the establishment of a duty to disclose information, are reviewed by Andrews and Reilly. There will be imperfect tests, and the balance between creating problems for those left with equivocal results and producing good for those whose results are definitive will be difficult to strike, a point covered by several of the participants in this symposium.

The questions raised by the audience attending this symposium range from technical to financial. They demonstrate that dialogue within the community is not only possible but that it is stimulating and useful. It must continue on formal and informal levels if the goals noted at the beginning of this symposium are to be met. It is hoped that this symposium and others like it will arouse the interest of the medical community and the public so that the promise of the new genetic technology will become a reality.

SUMMARY

Technology for newborn and population screening for genetic conditions has expanded rapidly over the last decade. The powerful new techniques of molecular genetics promise to improve the health and well-being of infants yet unborn. The development of specific molecular technology for the diagnosis of such genetic disorders as sickle-cell anemia and cystic fibrosis will have major influence on the medical and public health community. In order effectively to provide care and guidance for their patients, physicians, nurses, and other health care providers will need to be aware of the available tests, the crucial medical and counseling services, and the ethical, legal, and financial implications which apply to newborn and population screening. This symposium presents the current issues to health care professionals, in order to establish dialogue among groups involved and to stimulate community discussion.

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