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Newborn Screening for Cystic Fibrosis: A Paradigm for Public Health Genetics Policy Development

Proceedings of a 1997 Workshop

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Newborn Screening for Cystic Fibrosis: A Paradigm for Public Health Genetics Policy Development Proceedings of a 1997 Workshop

Summary

Cystic fibrosis (CF) is a genetic disease that can be detected in newborn infants (i.e., those aged ≤1 month) by immunotrypsinogen testing. The sensitivity and specificity of such testing can now be improved as a result of the recent discovery of the Cystic Fibrosis Transmembrane Conductance Regulatory (CFTR) gene. Although limited CF screening for newborns has been used since the 1980s, the clinical, social, and economic outcomes of population-based screening are controversial.

During January 1997, a workshop was convened at CDC in Atlanta, Georgia to discuss the benefits and risks associated with screening newborns for CF and to develop public health policy concerning such screening. The workshop planning committee comprised representatives from CDC, the Cystic Fibrosis Foundation, the National Institutes of Health, and the University of Wisconsin. Experts in the fields of CF, public health, the screening of newborns, and economics also contributed to discussions. Workshop participants addressed a) benefits and risks, b) laboratory testing, and c) economics concerning the implementation of routine CF screening for newborns. Summaries of these discussions and the resulting workshop recommendations are presented in this report. These recommendations, developed by workshop participants, will be useful to medical and public health professionals and state policymakers who are evaluating the merits of population-based screening of newborns for CF.

INTRODUCTION

As a result of the rapid advances in genetics technology and the Human Genome Project, most of the estimated 100,000 genes in humans will be identified by the year 2005 (*1*). More than 8,000 of these genes already have been identified or mapped (*2*). Yet, the application of genetics research in the promotion of health and the prevention of disease and disability has been explored only minimally. Information is lacking about the benefits and risks of genetic testing, the efficacy of early interventions, and the population distribution of genotypes and other risk factors associated with disease conditions. The complex and controversial issues concerning genetics research that have emerged (e.g., the quality of laboratory testing, the rapid commercialization of genetic tests, and the potential for discrimination and stigmatization) require public health leadership. Such leadership is needed to protect the public from inappropriate testing and to ensure that validated and useful tests are properly integrated into medical and public health practice. This endeavor is defined within the core functions of public health agencies proposed by the Institute of Medicine: assessment, policy development, assurance, and evaluation (*3,4*).

Screening tests for certain genetic diseases among newborn infants (i.e., those aged ≤1 month) currently are widely accepted and used. Since the development of the immunoreactive trypsinogen test (IRT) for cystic fibrosis (CF), experts in the field of CF have considered adding this test to the newborn screening panel. The discovery of the Cystic Fibrosis Transmembrane Conductance Regulatory (CFTR) gene (*5*) renewed interest in this possibility, as the sensitivity and specificity of testing could be improved through DNA-based testing. Although limited CF screening using IRT and molecular tests has been used among newborns since the mid-1980s, the clinical, social, and economic outcomes of population-based screening are still controversial.

Previous consensus symposia, held in 1983 and 1991, concluded that routine CF screening for newborns should not be widely implemented until the clinical benefits of such screening outweighed risks and justified costs. Since then, studies involving screening newborns for CF have continued, treatments for CF have evolved, and the public's interest in genetic testing has increased. Because CF is a genetic disease that affects one in 3,800 newborns, public awareness of CF can be expected to increase, generating more requests for CF screening. Academic and public health officials should be prepared to determine the appropriateness of population-based screening for newborns using newly developed genetic testing.

The goals of the workshop "Newborn Screening for Cystic Fibrosis: A Paradigm for Public Health Genetics Policy Development," convened at CDC in Atlanta, Georgia, were to a) encourage the collaboration of international leaders involved in CF research, clinical practice, public health, and the screening of newborns for a discussion of the benefits and risks of screening newborns for CF and b) discuss public health policy concerning such screening. The workshop planning committee comprised representatives from CDC; the Cystic Fibrosis Foundation; the National Institutes of Health; the University of Wisconsin; and experts in the fields of CF, public health, the screening of newborns, and economics. This workshop was open to the public and announced in the Federal Register. Workshop participants discussed a) benefits and risks, b) laboratory testing, and c) economics concerning the implementation of routine CF screening for newborns. The resulting recommendations, developed by workshop participants, will be useful to medical and public health professionals and to state policymakers who are evaluating the merits of population-based screening of newborns for CF.

BACKGROUND

CF is a chronically debilitating, autosomal recessive disease that affects the respiratory, gastrointestinal, and reproductive systems. It is the most prevalent, life-shortening, hereditary disease among white children, with an incidence ranging from 1 in 1,700 to 1 in 6,500 (*6*). In 1995, approximately 20,000–25,000 persons in the United States had CF (*7*).

Since the early 1960s, screening newborns for CF has been possible by measuring albumin levels in neonatal meconium (*8*), although this method is time consuming and cumbersome. Not until 1979, when the blood of newborns with CF was found to contain elevated levels of IRT, was large-scale screening considered possible (*9*). The IRT allowed screening to be done from a heel-stick blood spot. As a result of the availability of this test, some international screening programs were implemented. In

addition, Colorado, Wisconsin, and Wyoming began pilot CF screening programs for newborns that evolved into comprehensive screening and testing programs.

In 1989, the CFTR gene was cloned and mapped to chromosome 7 (*5*), which allowed newborns to be screened through direct DNA testing. This advance resulted in screening results with greater sensitivity, specificity, and positive predictive value and created the potential for genetic testing to become diagnostic, thus replacing clinical judgement and ionophoretic sweat testing. However, the genotype-phenotype correlations for CF were difficult to elucidate. In addition, more than 600 mutations of the gene have been identified, making it difficult to study each one.

The potential for the nationwide screening of newborns in the United States has been examined by several expert panels. In 1983, the Task Force of the Cystic Fibrosis Foundation (CFF) (*10*) and the American Academy of Pediatrics (*11*) concluded that more clinical data were needed regarding the impact of CF screening for newborns and the validity of the IRT test before nationwide CF screening programs could be implemented. One of the main concerns was that early social and medical interventions may not benefit presymptomatic children and could instead harm them, because no therapy is without risk. After the discovery of the CFTR gene, these issues became more complex because health officials realized that genetic testing also could identify carriers of the defective gene and clinically healthy or mildly affected persons having two copies of this gene. Decisions concerning how to clinically and ethically handle these new situations and other issues related to whether population-based newborn screening for CF is appropriate in the United States were addressed by the workshop participants.

WORKSHOP OBJECTIVES AND AGENDA

The workshop entitled "Newborn Screening for Cystic Fibrosis: A Paradigm for Public Health Genetics Policy Development" was designed to achieve the following five objectives:

- review the available clinical data from current studies of and programs for the screening of newborns for CF;
- assess the types of clinical, epidemiologic, and health-care delivery data needed to develop public health policy concerning CF screening for newborns;
- review the benefits and risks of screening newborns for CF, both for individuals and for society;
- review the current state of laboratory screening technology and other laboratory issues surrounding implementation of population-based screening of newborns for CF; and
- assess the infrastructure and program design of existing screening programs to better plan for other potential screening programs.

Workshop participants were asked to recommend areas for further study and to evaluate the social, ethical, clinical, public health, and economic implications of instituting population-based screening for CF in the United States. Following the plenary sessions, which provided background information and raised basic concerns,

workshop participants divided into three work groups to develop recommendations addressing these topics. Rapporteurs then presented the work group findings and work group recommendations in reassembled plenary sessions. This report includes the abstracts of the presentations (which are presented by benefits and risks, laboratory issues, cost-effectiveness, and international programs), the individual work group summaries and recommendations, and the overall conclusions and recommendations.

SUMMARY OF PLENARY PRESENTATIONS

Benefits and Risks

An Epidemiologic Evaluation of Newborn Screening for Cystic Fibrosis: A Scientific Challenge for Public Health Action—Joanne Cono, M.D., Sc.M., Muin J. Khoury, M.D., Ph.D., *National Center for Environmental Health, CDC*

Since 1989, interest in population-based CF screening for newborns has increased in the United States. Although some countries and U.S. states (i.e., Wisconsin, Colorado, and Wyoming) have screened neonates for CF since the mid-1980s, other U.S. states have been waiting to ensure that substantial clinical benefits are demonstrated by controlled clinical trials. We applied epidemiologic principles to evaluate the ability of observational studies and controlled clinical trials to determine the effects of screening newborns for CF. Although results of observational studies suggest clinical benefits from early diagnosis of CF, these results are difficult to interpret because of the potential for confounding bias (i.e., the apparent benefits may be associated with factors other than newborn screening), selection bias (i.e., the screened and unscreened groups may not adequately represent their respective underlying populations), and lead-time bias (i.e., the screened group may appear to have a higher survival rate because of a greater time interval between diagnosis and death). We also assessed the likelihood that a controlled clinical trial could demonstrate the benefit of early detection by performing power calculations to evaluate the number of subjects needed in such a study. Expected rates of various mortality and morbidity outcomes were derived from the 1994 Cystic Fibrosis Foundation Patient Registry Annual Data Report. Using $\alpha = 0.05$ (two-sided test) and $\beta = 0.20$, a total of 2,105 newborns with CF would be needed in both the case and control groups to measure a 50% reduction in mortality associated with a particular intervention before the age of 5 years among newborns who have a baseline annual mortality rate of 2.2%. For a 50% reduction in deaths caused by CF before the age of 10 years (mortality rate: 4.4%), 1,034 children would be needed in each group. For a 50% reduction in rates of more common endpoints of growth and morbidity (i.e., baseline rates of $\geq$25%), only 143 newborns with CF would be needed in each group (Table 1). In a hypothetical clinical trial conducted in a region where the incidence rate of CF among white infants was 1 in 3,400 and 100,000 white infants were born annually, the trial would have to be conducted for >50 years to detect a 50% reduction in mortality for children aged <5 years. Thus, unless substantial reductions in morbidity and mortality are observed, a regional clinical trial may not be useful in assessing the clinical utility of screening newborns for CF within the next 10 years. If public health action is dependent on the results of small clinical

TABLE 1. Sample sizes needed to detect a 50% reduction in morbidity and mortality* among persons with cystic fibrosis

	Baseline rate	Number
Age at death		
< 5 years	2.2%	2,105
<10 years	4.4%	1,034
<15 years	10.6%	408
Growth		
Weight†	26.3%	143
Height†	20.6%	192
Morbidity		
Failure to thrive	30.6%	94
Less than one hospitalization	35.8%	95

*Using the values $\beta = 0.20$, $\alpha = 0.05$, and a two-sided test; based on the 1994 Cystic Fibrosis Patient Registry Annual Report.
†Less than the fifth percentile.

trials, the implementation of CF screening programs for newborns may never progress—even if analyses of screening outcomes demonstrate clinical benefits. Because of the methodologic problems associated with observational epidemiologic studies and the limited sample sizes available for regional clinical trials, public health officials face the possible dilemma of making public health policy recommendations concerning the screening of newborns for CF without adequate data regarding the efficacy of such screening.

Update on Medical, Genetic, and Surgical Therapies for Cystic Fibrosis—Bonnie W. Ramsey, M.D., *University of Washington*

CF pulmonary disease is associated with viscous, purulent secretions. The cornerstones of CF treatment have been correction of pancreatic insufficiency by enzyme replacement; reversal of secondary nutritional and vitamin deficiencies; treatment of obstructive lung disease by clearance of lower airway secretions; and treatment of secondary pulmonary infections with appropriate antimicrobial therapy and adjuvant anti-inflammatory, bronchodilatory, and mucoactive agents (*12*). Agents that reduce the viscoelastic properties of sputum have long been advocated to improve airway clearance. A new mucoactive agent, rhDNase, developed with recombinant technology, has demonstrated efficacy in reducing both airway obstruction in patients with CF and the risk for respiratory exacerbations requiring intravenous antibiotics (*13*). The enzyme has been available for patient use since 1994 and is safe at the recommended dosage of 2.5 mg per day by inhalation.

Patients with CF experience periodic pulmonary exacerbations, which are identified by increased pulmonary symptoms and airway secretions. Standard therapy for such exacerbations is parenteral administration of two antibiotics for 14–21 days, intensified airway clearance, and other adjuvant therapies (e.g., use of bronchodilators or antiinflammatory agents) (*14*). Traditionally, the use of long-term prophylactic antibiotics has been advocated potentially to reduce the frequency of pulmonary

exacerbations. However, use of oral antistaphylococcal prophylaxis has not substantially reduced the frequency of exacerbation or progression of lung disease and may increase the patients' risk for developing antibiotic-resistant bacteria (*12,15*). The use of inhaled antibiotics by patients with CF is appealing to health-care providers because high concentrations can be delivered directly to the site of infection with low systemic absorption. Patients receiving high-dose tobramycin therapy have had improved lung function and a 99.9% reduction in sputum bacterial density (*16*). Use of other inhaled antibiotics (e.g., colistin) is being studied (*17*).

Lung infections in persons who have CF are associated with an intense inflammatory (predominantly neutrophilic) response. Therapeutic interventions to modulate this inflammatory response have become increasingly popular. Ibuprofen, a nonsteroidal antiinflammatory agent that inhibits migration and activation of neutrophils, has been studied. Of 85 patients with CF, patients taking ibuprofen demonstrated less decline in FEV1 than did those taking a placebo (*18*); the greatest effect occurred among children aged 5–13 years. Effective use of this therapy requires regular monitoring of serum ibuprofen concentrations.

No biologic or pharmacologic therapies directed at the primary chloride channel defect currently are available. However, several early (i.e., Phase I and Phase II) trials among humans are in progress involving gene therapy and pharmacologic approaches to ameliorate or bypass the primary defect. Several gene transfer systems, both viral and non-viral based, are being developed to deliver CFTR cDNA to the airway (*19*). Several pharmacologic approaches also are being tested as means of improving CFTR function; these approaches involve augmenting trafficking of the protein to the apical membrane, improving activation of the mutant CFTR protein, and bypassing CFTR-mediated chloride transport and using alternative channels.

Clinical Course of Infants with Cystic Fibrosis: Opportunities for Early Intervention—Frank J. Accurso, M.D., Marci K. Sontag, M.S., *University of Colorado School of Medicine*

Identification of newborn infants as having CF through IRT-based screening has allowed researchers to examine the early stages of the disease. A wide range of abnormalities have been identified among infants with CF. Infants with CF have abnormal growth, nutritional status, and pancreatic function by age 2 months (*20–22*). Protein calorie malnutrition continues to occur in infants with CF (*23*). Specific viruses—especially the respiratory syncytial virus—have been identified in infants with CF who were hospitalized for respiratory problems (*24*). Studies of both the upper and lower airways have demonstrated that infants with CF identified by screening during the newborn period have evidence of infection with common pathogens—*Staphylococcus aureus*, *Hemophilus influenzae,* and *Pseudomonas aeruginosa* (*25,26*). In addition, neutrophil-dominated inflammation is present in the early stages of CF, and in some cases, without evidence of concomitant infection (*20,21*). These findings identify several opportunities for early treatment of CF, including better nutritional interventions aimed at improving growth in infancy. In addition, protein calorie malnutrition may be a preventable complication of CF if diagnosis and treatment with pancreatic enzymes are implemented early. Treatment trials of antiviral agents also should reduce respiratory morbidity among infants. Because infants with CF have pathogens and inflammation in their lower airways, treatments for infection and

inflammation may need to be started in infancy to slow the development of the progressive, suppurative lung disease that occurs in later life. Because persons who have CF and who are infected with *P. aeruginosa* have more rapid deterioration of lung function, and because the survival rate of such patients is improved in centers in which *P. aeruginosa* is aggressively treated, reducing the colonization rate of this pathogen is an important goal in early treatment (*27*). In summary, clinical evidence that almost every feature of CF occurs during the newborn period suggests the need for early diagnosis and treatment. Controlled clinical trials are needed to demonstrate the benefits of early intervention.

Issues in Implementation of Newborn Screening for Cystic Fibrosis—Drucy S. Borowitz, M.D., *State University of New York at Buffalo*

CF is an autosomal recessive disease that is chronic, progressive, and life limiting. More than 700 mutations of the gene that causes CF exist, but even among patients having the same genotype, disease severity varies widely. Most of the approximately 25,000 persons in the United States with CF are followed at care centers accredited by CFF (*28*). These 114 centers conform to national standards, and data collected for patients followed at such centers are submitted to the CFF National Registry.

Currently, CF is diagnosed clinically. In 1995, approximately 60% of patients with newly diagnosed CF were aged <1 year, and 90% were aged <15 years. When patients are diagnosed and referred to a CF care center, a team of professionals (including physicians, nurses, social workers, nutritionists, respiratory therapists, and genetic counselors) help families cope with the diagnosis, educate them about the disease, and begin therapeutic interventions.

In the United States, an estimated 80% of persons with CF are followed at CF care centers (*6*). If newborn screening were instituted, the increased case ascertainment likely would not require substantial additional care resources. However, the identification of presymptomatic patients by screening during the newborn period might lead managed care systems to limit access to CF care centers. Because few objective outcomes can be measured among children aged <5 years with CF, expert monitoring for subtle changes in disease course is critical. Effective communication between state screening programs and CF care centers will be essential if newborn screening is implemented. Reporting to CF care centers and state health authorities ideally would be accomplished by legislative mandate.

Some schemes for screening newborns include a tier of genetic testing that will, as a secondary effect, identify CF carriers. If a state implements a CF screening program for newborns that includes mutation analysis, adequate numbers of genetic counselors must be made available to discuss test results with CF carriers. Studies have demonstrated that families at high risk for having a child with CF make reproductive choices based on knowledge of carrier status. However, CF care centers do not have the resources to offer genetic counseling to families that do not have a child with CF.

Design and Execution of the Wisconsin Cystic Fibrosis Newborn Screening Trial—Michael R. Kosorok, Ph.D., Philip M. Farrell, M.D., Ph.D., the Wisconsin Cystic Fibrosis Neonatal Screening Study Group, *University of Wisconsin, Wisconsin State Laboratory of Hygiene, and Medical College of Wisconsin*

The Wisconsin newborn screening project is a randomized clinical trial that provided data concerning the benefits and risks of CF screening for newborns. All infants born in Wisconsin from April 15, l985 through June 30, 1994, were randomly assigned to either a screened (i.e., early diagnosis) or control (i.e., standard diagnosis) group. Randomized group assignment was determined by the last digit of the state laboratory number assigned to the blood-spot specimen. The CF status of all infants was determined by a sweat chloride test after screening with either a single-tier IRT or two-tier IRT/DNA assay. For those infants randomly assigned to the screened group, positive results were reported to the parents, who were urged to obtain a sweat test. For those infants randomly assigned to the control group, results of the assay were stored in a database and reported when the child was aged 4 years (unless a CF diagnosis had been made). An active surveillance system was developed, and a policy and data monitoring board was established to monitor the integrity and safety of the study. The ethical issues involved in this design have been published elsewhere (*29*).

A total of 143 cases of CF were either diagnosed through screening during the newborn period or, for infants who tested false-negative on the screening test, diagnosed on the basis of signs and symptoms. The average age at diagnosis for patients without meconium ileus was lower in the screened group (mean=12.7 weeks) than in the control group (mean=80.6 weeks; $p<.001$). The overall age distribution of the control group was not substantially different from the total U.S. population of patients with newly diagnosed CF, as reported in the CFF Registry. Primary pulmonary outcomes were evaluated on the basis of Wisconsin chest radiograph scores and pulmonary function data. Primary nutritional outcomes were evaluated on the basis of age-adjusted height and weight. These outcomes were stratified by meconium ileus status, pancreatic functional status, sex, age, and center (i.e., Madison or Milwaukee). The data were analyzed regularly by using the procedure for analysis of covariance for repeated measures; the treatment group was the main effect of interest and the stratification variables were covariates. The original sample-size calculations determined that approximately 45 patients per treatment group would be needed to detect a clinically significant difference with 80% power for a type I error of 5%. Nutritional status assessment has been completed, but because data accrual for the pulmonary outcomes has been time consuming, these outcomes have not been analyzed; sufficient data should be available to complete these analyses during 1998.

Assessment of the Benefits, Risks, and Costs of Cystic Fibrosis Newborn Screening in Wisconsin—Philip M. Farrell, M.D., Ph.D., Michael R. Kosorok, Ph.D., Michael J. Rock, M.D., the Wisconsin Cystic Fibrosis Neonatal Screening Study Group, *University of Wisconsin, Wisconsin State Laboratory of Hygiene, and Medical College of Wisconsin*

In 1985, comprehensive evaluation of CF screening among newborns was implemented as a randomized trial in Wisconsin's two CF centers to address the hypothesis that neonatal screening for CF would be beneficial without posing major risks. Our results indicate that biochemical evidence of inadequate nutrition is common at

diagnosis in infants who are screened for CF as newborns (i.e., the screened group) and in those diagnosed as having CF on the basis of signs and symptoms (i.e., the control group), but that therapy corrected low levels of serum albumin and fat-soluble vitamins. Infants in the screened group who did not have meconium ileus were on average in substantially higher height and weight percentiles at diagnosis. Statistical analyses assessing the 10-year follow-up period revealed that the screened group also scored substantially higher on anthropometric indices. Repeated measures analysis using Generalized Estimating Equation methods with an independence working correlation matrix, logit link, and binary variance (*30*) was performed to assess differences between the screened and control groups in the proportion of children below the 10th percentile for weight and height. This analysis was conducted for all data available through October 15, 1996. Analyses were adjusted for the covariates of age, sex, CF center, genotype, pancreatic status, birth weight, and age at diagnosis; analyses also were adjusted for the influence of the patient's sex on these covariates. Children in the control group were 3.06 times more likely to be below the 10th percentile of weight (confidence interval [CI]=1.29, 7.22; p=0.011) and 3.54 times more likely to be below the 10th percentile for height (CI=1.29, 9.71; p=0.014).

The risk assessment component of this project included several psychosocial issues. Our results indicate that short-term anxiety and anger can occur in families of infants testing false-positive, and that adequate communication is essential in alleviating the concerns of these families. An associated study of stress among mothers whose infants had false-positive screening results revealed that such mothers had less stress but greater anxiety compared with mothers of infants testing negative for CF.

One medical risk for young children with CF is acquisition of *P. aeruginosa*. Overall, no differences in acquisition of respiratory pathogens existed between the screened and control groups. Evaluation of the data between and within the two centers, however, revealed that the following risk factors are associated with an earlier acquisition of *P. aeruginosa* in screened patients: urban location; having newly diagnosed, young children and older CF patients in the clinic at the same time; and social situations in which CF patients interact. These results suggest that clinical exposures or social interactions may predispose patients with CF to *P. aeruginosa* infection, and that segregated clinics may be appropriate for young children who are diagnosed through screening as having CF.

Newborn Screening Informed Consent Issues—Linda McCabe, Ph.D., Edward R.B. McCabe, M.D., Ph.D., *University of California at Los Angeles*

Screening programs for newborns were established in response to the activism of parents of children with PKU. Such parents did not want their children to go untreated and thus become mentally retarded from the phenylalanine in a normal diet, when initiation of a low phenylalanine diet early in the newborn period would ensure normal intellectual development. Every state has a screening program for newborns that includes PKU, congenital hypothyroidism, and other disorders. The disorders screened for among newborns and the requirements for informed consent vary from state to state. State standards vary from informed dissent to extensive education before informed consent. Several recent position papers regarding informed consent for genetic testing have implications for the screening of newborns. Among these are a

document and an accompanying editorial in *Diagnostic Medical Pathology* prepared by participants in the National Center for Human Genome Research (now the National Human Genome Research Institute) and the CDC-sponsored workshop. Other position papers include statements from the American College of Medical Genetics (ACMG), the American Society of Human Genetics (ASHG), and the ACMG/ASHG joint statement on genetic testing in children (*31–35*). The widely disparate views expressed in these papers have different implications for informed consent for the screening of newborns. Some suggest that no persons aged <18 years should be tested unless they receive immediate medical benefit, whereas others recognize the varying ages at which children become responsible for their own health-care decisions. Concern about the exclusion of children from clinical research led the National Institute of Child Health and Human Development and the American Academy of Pediatrics to sponsor a workshop in 1996 entitled "Inclusion of Children in Clinical Research" (*36*). Because of the implications the positions of these agencies have for informed consent for CF screening among newborns, the effects of statewide programs for the screening of newborns and the costs and benefits that CF screening for newborns may have on both the immediate and long-term health of infants with CF must be considered.

Ethical Issues in the Development of Public Health Policy for Newborn Screening: The Experience with Cystic Fibrosis—Benjamin S. Wilfond, M.D., *University of Arizona*

The health-policy decision to establish a new program for the screening of newborns is the result of clinical, sociopolitical, and ethical considerations that can be evaluated through two complementary models: the extemporaneous model and the evidentiary model (*36*). The extemporaneous model is descriptive and acknowledges the role of professional practice and legal, market, and consumer forces in determining the standard of care. The evidentiary model is prescriptive and suggests that empirical data are necessary before making a health policy decision. However, the thrust of the evidentiary model is that data alone are insufficient because of additional normative assessments that refer to decisions about value: the value of the intervention or the value of the data about the intervention. Such decisions should include both public input from survey or focus-group research and public representation on regional or national advisory committees. The evidentiary model draws attention to several emerging policy issues regarding the normative evaluation of the benefits and risks of CF screening for newborns.

The potential therapeutic benefits of screening newborns for CF can be maximized by ensuring that all children identified as having CF have access to comprehensive treatment centers. However, additional data must be collected as treatments change. For example, an effective therapy for CF might further enhance or mitigate the value of screening newborns for CF. Thus, one of the benefits of screening newborns is the identification of subjects for trials of early interventions.

Although children with CF would benefit by screening tests, the greatest harms may be transient distress or long-term confusion among families who have infants with false-positive results on screening tests. More data are needed about approaches to genetic counseling and follow-up of infants who test false-positive for CF and are identified as carriers. Further consideration should be given to improving the

informed consent process, particularly when carriers are identified. Families of children testing false-positive should be involved in making health-policy decisions.

The benefits of screening newborns for CF should be prioritized within the context of other services for families with CF-affected children. For example, if additional public fiscal resources are available for CF care, these resources could be expended for newborn screening for improved access to primary medical and hospital care or for outpatient nursing; respiratory therapy; and nutritional, vocational, and social work services. The benefits also should be considered within the context of other potential health care and social benefits for all children (e.g., prenatal care, vaccinations, and primary care).

Weighing the benefits and risks of screening newborns, as a normative policy issue, requires broad public participation. Families of persons with CF, families of children testing false-positive for CF, and the general public should be involved in making policy decisions.

Laboratory Issues

Comparison of Newborn Screening Methods and Use of the Sweat Test for Diagnosis of Cystic Fibrosis—Philip M. Farrell, M.D., Ph.D., the Wisconsin Cystic Fibrosis Neonatal Screening Study Group, *University of Wisconsin, Wisconsin State Laboratory of Hygiene, and Medical College of Wisconsin*

We evaluated the screening of newborns for CF for approximately 10 years in Wisconsin. We studied screening procedures used and characteristics of infants who tested false-positive for CF. One objective has been the comparison of a single-tier IRT screening method with a two-tier method in which IRT testing and DNA analyses are used to detect the most common mutation (i.e., ΔF508) responsible for CF. We also examined the benefit of including up to 10 additional CFTR mutations in the screening protocol. From 1985 through 1994, a total of 220,862 neonates were screened by the IRT protocol, and 104,308 neonates were screened by the IRT/DNA protocol. For the IRT protocol, neonates with an IRT ≥180 ng/mL were considered positive; these infants then had a standard sweat chloride test to determine CF status. For the IRT/DNA protocol, samples from the original dried neonatal blood specimen with IRT ≥110 ng/mL were tested for the presence of the ΔF508 mutation; if the DNA test revealed one or two ΔF508 alleles, a sweat test was obtained. Investigation of sweat test procedures in infants aged ≤1 year was performed, revealing that quantitative iontophoresis can be successfully and reliably used to assess the sweat chloride levels of children aged <6 weeks. We also observed that a diagnostic cut off of 40 mEq/L is most appropriate and that sweat tests should be performed and interpreted with caution—particularly tests of CF heterozygote carriers (*37*). Our results indicated that both screening methods yield high specificity. Sensitivity was higher with the IRT/DNA protocol, but the differences were not statistically significant. The IRT/DNA two-tiered test had the highest sensitivity of all current newborn screening tests. The positive predictive value of the IRT/DNA screening protocol, however, was 15.2%, and the positive predictive value of the IRT protocol was only 6.4% ($p<.05$). Assessment of the population testing false-positive for CF by the IRT/DNA method revealed that the two-tier method eliminates the disproportionate number of infants with low Apgar scores and the high prevalence of blacks identified previously in our study of newborns with high IRT levels. We

observed that 55% of infants testing positive for CF by the DNA method were homozygous for ΔF508, and 40% had one such allele. Adding analyses for 10 more CFTR mutations has only a minimal effect on sensitivity but would add substantially to the cost of screening. Advantages of the IRT/DNA protocol over IRT analysis include improved positive predictive value, reduction in the number of infants testing false-positive, more rapid diagnosis with elimination of recall specimens, and identification of CF heterozygote carrier families for genetic counseling. We also studied the costs involved in diagnosing CF on the basis of signs and symptoms. This analysis revealed that in Wisconsin, the average cost per case of CF diagnosed is similar to that of other newborn screening methods and standard diagnostic procedures.

Comparison of Screening Strategies: The Value of Repeat IRT Testing—Keith B. Hammond, M.S., *University of Colorado*

The first published protocols for newborn screening using dried-blood spot (DBS) IRT measurements were based on the observation that infants with CF had elevated levels of IRT that could persist for several months or longer, whereas levels in infants who tested false-positive usually returned to normal within the first few weeks of life. These protocols required that newborns with elevated IRT levels be retested at approximately 1 month of age. Only those infants with a persistent elevation of IRT were then referred for diagnostic sweat testing. Concerns regarding this strategy include the substantial number of false-positive results after initial screening, the parental anxiety provoked by the need to obtain a second blood sample, and the possibility of false-negative results from the second blood specimen from infants who have CF and have rapidly deteriorating pancreatic function. Several screening programs have adopted the use of a 'two-tier' test, whereby gene mutation analysis is conducted on DNA extracted from the initial blood spot. This method obviates the need for a repeat blood test and provides diagnostic confirmation of CF in some infants without the need for sweat testing. An unwanted side effect of this approach is the identification of both carriers and CF-affected infants. In addition, the sensitivity of screening based on the ΔF508 mutation alone may be compromised depending on the population frequency of other CF mutations.

During 1982–1995, a total of 203 of 718,507 infants born in Colorado who were screened for CF tested positive for the disease, for a calculated incidence of 1 in 3,539. Thirty-seven (18.2%) of these infants had meconium ileus during the newborn period. Because of the early clinical presentation and known variability of IRT values in such infants, screening is not considered relevant to the diagnosis of these cases. Of the remaining 166 infants known to have CF, 10 (6.2%) tested false-negative after initial screening. In 1985, a patient who tested positive on initial screening tested false-negative after repeat testing according to our original cut-off criteria. No additional false-negative results after repeat testing occurred after the cut-off level was lowered to include this patient. In addition to the infants with false-negative results, two infants with elevated IRT values were not followed up because of administrative errors.

Genotypes were obtained for 120 infants with CF who tested positive by IRT testing and who did not present with meconium ileus. Eight (6.7%) of these infants did not have an ΔF508 mutation and would have been missed if this had been the only mutation tested for. These omissions would have added to the observed false-negative rate of 6.2% after initial screening unless a lower cut-off level had been used to select

samples for mutation analysis. Although the actual IRT values are unknown for each of the 10 patients who tested false-negative after initial IRT screening, several patients had values close to the cut-off level, suggesting that they would have been included if this level had been lowered. However, two (20%) of the infants testing false-negative did not have a copy of the ΔF508 mutation (G542X/G551 and UNK/UNK), and two had IRT values considered within the normal range, indicating that in our population, regardless of the initial IRT cut-off level used, mutation analysis testing only for the ΔF508 mutation would have a sensitivity lower than that of repeat IRT testing.

Laboratory Testing Issues and Quality Assurance for Cystic Fibrosis Screening—
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Introduction of the DBS as a specimen source for phenylketonuria (PKU) in 1961 led to the development of screening programs for newborns that use blood droplets collected on filter paper (FP) from a heel-stick of newborns shortly after their birth. Effective screening of newborns through analyses of these DBS specimens, combined with follow-up diagnostic studies and treatment, helps prevent mental retardation and premature death. In the United States, DBS specimens routinely are collected from >95% of all newborns.

Two laboratory components that are necessary for the expansion of CF testing are standardization and quality assurance (QA). Standardization of procedures and parameters for testing help ensure that consistent, high quality services are provided by all laboratories. QA efforts are essential for documenting reliability and accuracy and for establishing that laboratory testing can be regarded with confidence by the public health community. Persons from CDC and those who screen newborns have standardized the performance of the FP matrix used for DBS collection to minimize variances and to control problems that the FP contributed to analytic methods. An approved national standard for DBS collection (*38*) specifically defines criteria for collecting blood on FP and for measuring the FP parameters needed for consistent performance. Approved guidelines for the use of sweat tests in confirming have been available since 1994 (*39*). A draft document for the national standardization of CF screening among newborns presently is under review by persons involved in the screening of newborns. The document provides guidance for several elements of CF testing, including those concerning DBSs. However, no certified reference material for IRT has been developed by an independent organization with experience in producing reference material.

Two proficiency testing surveys are being used to assure the quality of CF testing: the CAEN IRT QA Survey (France) and the Human Genetics Society of Australasia's Newborn Screening QA Program (New Zealand). QA services for DBS screening tests that will detect CF are not provided by the U.S. National Newborn Screening QA Program. Some assay comparability problems have been observed by the QA programs. The different types of QA test materials distributed by the two survey providers do not always produce equivalent testing outcomes. Different antibody specificities in the assay kits used by participants make it difficult to determine a concentration and to find a reproducible source of trypsin that yields comparable results around the selected cut-off values for all assays. The appropriate number of DNA mutations for which to screen and the best method of simulating these mutations by QA materials

are undetermined. Currently, QA services only support measurements for ΔF508 alleles.

Although refinements and enhancements are needed for CF testing, the infrastructure for laboratory standardization is available to guide testing, and QA programs that monitor and document laboratory performance are operational. Therefore, laboratory standardization and QA issues should not impede the inclusion of CF screening in the present routine test panel for newborns. However, even with substantial laboratory standardization and excellent QA programs, the correct diagnoses for particular test results will in some cases be uncertain until case definitions for certain disorders associated with CF being targeted by the screening efforts can be specified.

Cost-Effectiveness

The Economic Impact of Population-Based Newborn Screening for Cystic Fibrosis—Noreen L. Qualls, Dr.P.H., M.S.P.H., Joanne Cono, M.D., Sc.M., Alison E. Kelly, M.P.I.A., Muin J. Khoury, M.D., Ph.D., *National Center for Environmental Health, CDC*

We assessed the cost-effectiveness of four newborn screening protocols for CF—two IRT/IRT/sweat test protocols (conducted in Colorado and Italy) and two IRT/DNA/sweat test protocols (conducted in Australia and Wisconsin) (*40–43*). Assessing the cost-effectiveness of four newborn screening protocols involved a) constructing a decision tree for each protocol; b) determining the positive predictive value and probability of compliance with each screening test; c) estimating costs of collecting blood specimens, performing the screening tests, and informing and educating families about test results for a 1-year period; d) deriving the average number of CF-affected newborns detected per 100,000 newborns tested; e) estimating two cost-effectiveness ratios—the average cost per newborn tested for CF and the average cost per newborn detected as having CF; and f) performing sensitivity analyses for uncertain cost and probability estimates. The average number of newborns with CF detected per 100,000 newborns tested was 17 in Colorado, 19 in Wisconsin, 27 in Italy, and 31 in Australia. The average cost per newborn tested for CF was $5.54 in Colorado, $5.68 in Italy, $5.80 in Australia, and $5.96 in Wisconsin calculated in 1994 U.S. dollars. The average cost per newborn detected as having CF was $18,710 in Australia, $21,037 in Italy, $31,368 in Wisconsin, and $32,588 in Colorado calculated in 1994 U.S. dollars. Under all newborn screening protocols, the average cost per CF-affected newborn detected increased as the probability of compliance with follow-up sweat tests decreased from 100% to 25%. In this specific application of decision analytic methods, the Australian newborn screening protocol was the preferred prevention strategy, because it detected the most CF-affected newborns at the least cost. However, the numerator of this cost-effectiveness ratio was less than the true cost for each protocol because it included only three of seven possible resource costs incurred by newborn screening, ignored costs associated with side effects of CF, and did not assign a monetary value to the time family members spent caring for a child with CF. In addition, the denominator also was an underestimate of the number of infants with CF, because it did not account for newborns with CF who were either missed in the initial screening or lost during follow-up. Prospective cost analyses and comparative longitudinal studies

should be conducted to more fully determine the costs and the effectiveness of newborn screening protocols for CF.

International Programs

Newborn Screening for Cystic Fibrosis in Northeastern Italy—Gianni Mastella, M.D., C. Castellani, M.D., *Regional Cystic Fibrosis Center, Verona, Italy*

In Italy, the first CF screening program for newborns began in the Veneto and Trentino Alto Adige regions in September 1973. A total of 1,291,600 newborns have been screened—an average of 56,000 per year. Currently, 98% of the population is being screened. Until 1981, screening was done by centralized determination of albumin on dried meconium by semiquantitative radial immunodiffusion assay (SQRID), and all samples testing positive were retested (*44*). In 1981, an IRT on DBSs was adopted based first on an RIA method, then on ELISA (*45*), then finally on DELFIA. In the early 1990s, a protocol was designed to verify to what extent mutation analysis on DBSs could improve the screening of newborns in an area with high allelic heterogeneity (e.g., Italy) (*46*). The protocol involved IRT estimation at birth, trypsin retesting after 1 month (RET), meconium lactase testing (LACT), and mutation analysis (MUT) of ΔF508, R1162X, and N1303K. IRT combined with LACT and MUT was a more sensitive screening method than IRT/LACT/RET and IRT/MUT. Consequently, in 1995, we adopted the following three-tier screening system: a) blood-spot IRT, b) LACT/MUT for samples testing positive by IRT, and c) sweat test for those testing positive by either LACT or MUT. We also developed and incorporated into the screening protocol a reverse dot-blot assay for 14 CF mutations, which enables the detection of 85% of local CF mutations. The cost of the IRT test, lactase assay, and sweat test is approximately $5.50 in U.S. dollars per child (including personnel and administrative costs). An average $ 0.50 U.S. per screened newborn must be added for mutation analysis, which is performed on about one case in 200, and another $ 0.50 U.S. must be added for genetic counseling for the families of CF carriers incidentally detected (about 1 in 2,700 persons tested) (*47*). Thus, the overall cost for diagnosing a case of CF is approximately $16,000 U.S.

The implementation of CF screening among newborns was concomitant with changes in CF epidemiology, including a) a substantial increase in the rate of diagnosis, which shifted the observed incidence of CF from one per 4,200 infants when the diagnosis was made by symptoms to one per 2,600 infants with the new screening protocol; b) a change in reproductive attitudes among parents of children with CF (in 1984, after diagnosis by screening and genetic counseling, 89% of parents with children with CF began using contraception, whereas only 48% of parents with children in whom CF was detected by symptoms did) (*48*), and c) an increased life expectancy (the probability of a child surviving to 23 years of age was approximately 25% in the prescreening period and increased to approximately 65% after screening was implemented).

We compared a cohort of persons with CF detected by screening with a cohort of persons with CF detected by signs and symptoms (*49*). Of 724,178 children born during 1973–1981, a total of 421,175 (58%) underwent CF screening as newborns by the SQRID system. The study suggested that during their first 16 years of life, the cohort of persons with CF who were diagnosed by screening had better outcomes than

persons who were diagnosed by symptoms or meconium ileus. Persons diagnosed by screening had lower mortality and better life expectancy (i.e., 38% overall death rate over 16 years in the meconium ileus group, 22% in the symptomatic group, and 8.6% in the screened and false-negative groups), less lung damage (i.e., better FEV1 values in the screened group of children aged 6–10 years), delayed *Pseudomonas* colonization (i.e., lower in the screened group than in the symptomatic patients during the first 8 years of life), and better nutritional status. However, preliminary evidence from studies of newborns diagnosed as having CF through screening should not be considered conclusive, as many biases and confounding factors exist in such studies.

Newborn Screening for Cystic Fibrosis in Australasia—Bridget Wilcken, M.B., Chb., *Royal Alexandra Hospital for Children, Sydney, Australia*

Before screening for CF started in Australasia in 1980, we documented a substantial delay between onset of symptoms and diagnosis of CF (*50*). By 1995, more than 3 million newborns had been tested. Currently, five of the six screening programs, covering 92% of the population, include a test for CF.

When the IRT protocol was used in New South Wales (NSW) with active surveillance for missed cases of CF, early diagnosis was achieved for 92% of cases (*14*). The positive predictive value after the first test was only 5% but improved to 47% after the second test. For the new IRT/DNA protocol, we predicted that, with 75% prevalence of the common mutation in persons with CF, we would achieve early diagnosis in 94%–95% of all case-patients (accounting for patients at high risk, negative IRT results, and negative DNA results). Results of our study have been consistent with our hypotheses. The false-positive rate with this strategy was low (0.05%), but some infants testing false-positive were CF carriers (i.e., unwanted carrier detection).

In NSW, we followed patients born in the 3 years before screening began and in the subsequent 3 years. We found a substantial decrease in the number of days patients spent in the hospital because of CF-related illness before age 2 years (from a mean of 27 days to a mean of 4 days); this decrease occurred suddenly, coincided with screening implementation, and showed no trend with time (*51*). When we followed 59 unscreened and 60 screened patients aged 5 and 10 years from this cohort, we observed that the age- and sex-adjusted standard deviation scores for weight and height were consistently higher among the screened patients, and that the scores of screened patients were no different from those of the reference population. The average predicted FEV_1, FVC, and FEF_{25-75} were substantially higher at age 5 and 10 years among the screened patients. At age 10 years, the average FEV_1 measurement was 10% higher (*52*).

The only adverse effect associated with CF screening for newborns was the unwanted detection of a minimal number of CF carriers. The age of children at the time of clinical diagnosis of missed cases was no different from that predicted, and studies indicated no problem with parent-child bonding or parent-child interactions.

In 1994, the incremental cost of adding CF screening to an already existing newborn screening program in NSW, including costs of genetic counseling and carrier testing for families of carriers inadvertently detected, was $1.50 Australian dollars per newborn screened (approximately $1.13 U.S.). The cost per CF-affected newborn detected, for infants not considered at high risk because of family history or meconium

ileus, was $5,160 in Australian dollars (*52*). Further cost calculations must include costs incurred by earlier treatment and costs avoided by reduced morbidity.

In Australasia, we determined that a two-tiered IRT/DNA protocol was an efficient strategy for case finding: it had a low false-positive rate but a false-negative rate of approximately 5%–6%. Substantial short-term benefits of early diagnosis and treatment have been demonstrated, and recent evidence suggests that benefits may persist for at least 10 years. Costs are balanced by short-term benefits.

Newborn Screening and Therapy for Cystic Fibrosis in the Netherlands—Jeannette E. Dankert-Roelse, M.D., Ph.D., *Free University Hospital, Amsterdam, the Netherlands*

Population-based CF screening for newborns has not been universally accepted as an important tool with which to improve the well-being of patients with CF. The early development of airways disease, however, suggests that early intervention often is necessary for patients to have prolonged survival in relatively good health, and the substantial increase in survival of persons with CF in recent decades implies that current therapies improve the outcomes for these patients. An experimental CF screening program for newborns based on the determination of the albumin content of meconium was conducted in the North of the Netherlands during March 1973–March 1979 for 45% of all newborns in the area. Because of its low sensitivity and specificity, however, this screening test was inadequate for mass newborn screening and was ended. During the next 10 years, we conducted a clinical follow-up study to evaluate whether early treatment started after diagnosis in newborns positively influences the long-term outcome and clinical condition of patients with CF (*53,54*). In another analysis, we compared three cohorts of patients with CF: a) 19 patients detected by screening (S cohort), b) 25 patients not screened and five patients not detected by screening (non-S cohort), and c) 32 patients born in the same area during the first 6 years after implementation of the screening program (post-S cohort) (*55*). Clinical data were analyzed by multivariate regression. Median age at diagnosis was <1 month in the S cohort and 14 and 23 months in the non-S and post-S cohorts, respectively. The frequency of CF in the S cohort was lower than in the non-S cohorts. Without screening, the diagnosis of CF is delayed in a substantial number of patients. Survival analysis of all patients (except those with meconium ileus) conducted 11 years after they were born revealed that only 65% of the non-S cohort survived, whereas 94% of the S cohort did. The S cohort had greater height and weight than the two other cohorts and less decline in lung function, expressed as FEV1%pred, than the non-S cohort. During the follow-up period, we also investigated the effects of early diagnosis and genetic counseling on family planning. We found that 10 siblings of non-S cohort members were born after the cohort member was found to have CF (and that two of these siblings had CF), whereas one sibling of an S cohort member was born during this interval. The number of children born to families with CF who received genetic counseling was substantially lower than the number estimated for the general population; in the S cohort, this reduction was greater than in the non-S cohort. We conclude that treatment for CF should begin before airways disease has caused irreversible damage. An early diagnosis through the screening of newborns allows a) parents to receive timely information regarding risk for recurrence and b) parents and health-care workers to ensure that the affected child receives appropriate nutrition

and begins pulmonary treatment before the development of advanced airways disease, thus leading to longer preservation of the child's lung function.

WORK GROUP SUMMARIES AND RECOMMENDATIONS

Benefits and Risks of CF Screening for Newborns

- Direct benefits to the CF-affected child should be the prerequisite for newborn screening programs.
- Available information from the ongoing, randomized clinical trial in Wisconsin suggests that screening newborns for CF may be beneficial by enhancing short-term nutritional status over a 5- to 10- year period. The significance of this benefit should be studied further.
- Observational studies suggest an association between poor growth and more severe lung disease in populations of CF-affected patients investigated in recent epidemiologic studies.
- Observational studies also have demonstrated that infants who are diagnosed as having CF as newborns through screening have pulmonary function that is similar to or better than that of those who are diagnosed later.
- Secondary benefits of screening newborns for CF include the following: a) reduced anxiety of parents associated with delayed diagnosis; b) genetic counseling for parents; c) new opportunities for clinical research, particularly randomized clinical trials, and a better understanding of the natural history and pathophysiology of CF; and d) other benefits available through follow-up at a CF center (e.g., access to new treatments).
- The potential harm of screening newborns is associated primarily with adverse psychologic reactions among parents of infants whose test results are false-positive. This potential problem is of concern when CF heterozygote carriers are identified with the IRT/DNA method. When CF heterozygote infants are identified, appropriate genetic counseling must be provided to families to ensure that they understand the meaning of "carrier status."
- As with all newborn screening programs, children whose test results are false-negative may be harmed by a delay in diagnosis. Although no evidence has been reported to suggest that further delay in diagnosis occurs as a result of CF screening, such a delay is a hypothetical concern for persons involved in screening programs for newborns and provides justification for physician and parent education.
- The development of CF screening programs for newborns will lead to unique challenges for almost all states. Patients' access to CF centers must be ensured, and screening laboratories and CF centers must have good rapport and effective collaboration.

- Because of the short-term nutritional benefits for persons with CF diagnosed through newborn screening and the long period of planning required for implementing screening programs for newborns, it would be appropriate for some states to initiate pilot research projects of CF screening among newborns (see Overall Workshop Recommendations).

Laboratory Issues Regarding CF Screening for Newborns

- The use of multiple IRT tests is associated with high false-positive rates that contribute to anxiety among family members and create added expenses for collection of a second specimen. Selection of an appropriate cut-off value for the second IRT analysis can help minimize false-positive test results. A potential benefit of IRT testing over DNA testing is that CF heterozygote carriers are not identified.
- The use of IRT testing in combination with DNA testing will reduce the number of false-positive results and likely the number of sweat tests performed. This combination testing improves the positive predictive value of test results and provides more rapid diagnosis with fewer recall specimens.
- Each screening program should determine allele frequencies in the population of patients with CF and determine the number of mutations for which to be tested by the DNA testing scheme. The preferred number of mutations for which to be tested will change as the result of new technology and the experiences of the screening programs.
- State-sponsored and other screening programs may limit their exposure to liability by stating which alleles are tested for in their rules and regulations for program operations. All cases of CF will not be identified by laboratory testing. Clinicians should be educated and informed to help manage program-specific test results and to understand testing limitations.
- The elements required for quality CF testing generally are the same as for other disorders. Laboratories must ensure the methods they use are validated in the clinic and in the laboratory. Laboratories must be certified under the Clinical Laboratory Improvement Act of 1988 (CLIA '88). Testing must be performed in a CLIA-licensed laboratory with appropriate standards of practice, quality control and performance monitoring, and documentation. Analytic kits approved by the Food and Drug Administration for CF testing should be used when available.
- Laboratories that screen for CF must participate in external performance (i.e., proficiency) testing that provides a frequent test challenge (i.e., proficiency testing that meets CLIA requirements). The QA test materials should simulate patient materials as closely as possible (as do DBSs for the testing of newborns). The U.S. National Newborn Screening Quality Assurance Program should expand its services to include QA testing for CF among newborns. The CF screening program should maintain an active audit of identified and missed cases.

- International reference materials are not available for IRT. The U.S. National Newborn Screening Quality Assurance Program has experience with criteria for certification and development of such reference materials for DBS tests. The reference material should be available in the DBS matrix. Production of this reference material should be pursued even as recommendations for immediate expansion of CF testing are being considered.
- The requirements for adding CF testing to the laboratory will be analogous to requirements for adding testing for any new disorder to newborn screening programs. Resources will be required for laboratory space, personnel, equipment, data processing, and follow-up and clinical case management. These resource needs will be reduced, however, if CF testing is added to an existing population-based screening program.

Economics of Newborn Screening for CF

- States deciding to implement CF screening among newborns can minimize the cost, particularly that of blood-specimen collection, by adding CF screening to an existing newborn screening program. The process for providing parent education and obtaining consent (if required) should be the same as already established for other newborn screening tests within the state.
- An IRT/DNA/sweat test screening protocol is preferred to an IRT/IRT/sweat test screening protocol because of reduced follow-up costs associated with repeated blood-specimen collection.
- To better understand the costs associated with not screening newborns for CF (i.e., clinical diagnosis of CF), the University of Wisconsin should complete an economic analysis (e.g., a retrospective cost-benefit or cost-effectiveness analysis) of its randomized, clinical trial.
- To better enumerate the costs associated with CF screening for newborns, screening programs should clearly identify the costs associated with newborn screening activities and those associated with follow-up care and treatment services (e.g., sweat-test costs should be considered part of newborn screening, whereas CF carrier counseling costs should be part of follow-up care and treatment).
- Other newborn screening programs (e.g., PKU) may be viable sources for needed cost information about CF screening for newborns.
- Potential long-term savings resulting from screening newborns for CF include those associated with a) reductions in the number of hospitalizations for CF-related respiratory illnesses, b) treatments for respiratory syncytial virus-related morbidity, and c) maintaining CF-affected children's nutritional status as opposed to having to "catch up" to improve it.

OVERALL WORKSHOP CONCLUSIONS AND RECOMMENDATIONS

The 1997 workshop, "Newborn Screening for Cystic Fibrosis: A Paradigm for Public Health Genetics Policy Development," resulted in several recommendations. First, before recommending universal CF screening for newborns as a routine public health intervention, policymakers will need more compelling data about its effectiveness. This evidence might include a better description of the consequences of delayed diagnosis, information regarding cognitive development differences caused by malnutrition, data establishing pulmonary benefits of early diagnosis, and the cost-effectiveness of early diagnosis through screening. Second, because nutritional status has been identified as being potentially affected by the screening of newborns for CF (*56,57*), CFF should consider adding this parameter to its patient registry in the form of a data line to record edema and hypoproteinemia. Third, a meta-analysis should be performed on outcome data for the screening of newborns for CF collected from Colorado, Wisconsin, Australasia, the Netherlands, and Italy; clinical trial data should be separated from observational study data. Fourth, within 2 years, a national consensus panel should be convened to review and translate the results of the completed Wisconsin longitudinal study, make recommendations, and provide advisory support to individual states attempting to initiate screening programs for newborns. Fifth, further longitudinal studies of the impact of early intervention resulting from screening newborns for CF should be conducted and should focus on the impact of early nutritional status on neurodevelopment. Although a minimal risk exists for psychological harm to children falsely suspected of having CF and their families and a potential risk exists for delayed treatment for children falsely identified as not having CF, the Wisconsin controlled clinical trial presents evidence of nutritional benefits resulting from screening newborns for CF.

Finally, although the potential methodologic problems with observational epidemiologic studies and the limited sample size in regional clinical trials lead to dilemmas in generating data for formulating public health policy recommendations concerning CF screening among newborns, the workshop participants concluded that sufficient evidence exists to recommend pilot state-based demonstration programs. Public health research programs should use a multidisciplinary team approach in the design of such pilot studies. Team members should include clinicians, social workers, genetic counselors, nutritionists, laboratorians, and epidemiologists. Pilot CF screening programs for newborns should be approached and promoted as research endeavors, for which participation is not mandatory and informed consent is emphasized, and as community intervention programs that refer patients to accredited CF care centers. Pilot CF screening programs for newborns should include the following design attributes: a) genetic counseling for families with newborns who have CF or those who are carriers, b) referral to accredited CF care centers, and c) clinician education about the need for informed consent for testing newborns for CF. Such programs will create new opportunities for gathering data about the effects of different early intervention modalities on preventing morbidity, disability, and mortality associated with CF. In addition, these programs may decrease the anxiety many families now experience while they await diagnosis via traditional means. Finally, further

discussions are needed in the development, implementation, and evaluation of state-based pilot programs.

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