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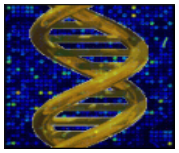

Virtual Office of Genomics

Issue Brief

July 2006

Universal Newborn Screening for Cystic Fibrosis in Connecticut?

Introduction

Newborn screening (NBS) has been a public health activity since testing for phenylketonuria began in the 1960's. Each state is responsible for designing and implementing its own NBS program. Each NBS program is a comprehensive system that includes parent and provider education, dried-blood-spot specimen collection and laboratory analysis, notification of abnormal screening results to health care providers, and follow-up activities including tracking of newborns from diagnosis to treatment. State health departments, diagnostic facilities, and treatment centers must be prepared to manage the children referred by screening.

Currently Connecticut does not include cystic fibrosis (CF) in its universal newborn screening program administered by the Department of Public Health (DPH). However, 20 out of 29 of the State's birth hospitals offer newborn screening for CF on a voluntary basis. Furthermore, a 2005 report prepared by the American College of Medical Genetics, commissioned by the Maternal and Child Health Bureau of the Health Resources and Services Administration of the U.S. Department of Health and Human Services, has proposed that 29 conditions, including CF, be included in a uniform newborn screening condition panel.[1] Although legislation has been proposed in the past few years to require newborns be tested for CF in Connecticut, it has not yet been passed.

The Centers for Disease Control and Prevention (CDC) published recommendations for newborn screening for cystic fibrosis in the October 15, 2004 *Morbidity and Mortality Weekly Report*.[2] They conclude that screening for CF is reasonably justified based on evidence of moderate benefit and low risk of harm. However, they also indicate that states must consider resource constraints and competing priorities.

A policy decision to add a disorder, such as cystic fibrosis, to the State's NBS screening panel should consider the State's responsibility for ensuring access to all components of the NBS system, not just the laboratory test. Expansion of NBS to include CF must, therefore, take into consideration the funding needed to support the integrated system.

Newborn screening has traditionally used biochemical testing methods to detect inherited disorders, such as phenylketonuria and galactosemia. Use of DNA testing is a more recent development. An unintended consequence of DNA testing, however, is that carriers♦ of genetic mutations are being identified. This heightens the importance of genetic counseling services for families. It also amplifies the controversial nature of CF newborn screening for public health policy.

Overview of Cystic Fibrosis

Cystic fibrosis is a life-threatening, genetic disease that can cause severe lung damage and nutritional deficiencies. With cystic fibrosis, a defective gene, known as the cystic fibrosis transmembrane conductance regulator (CFTR) gene, causes the body to produce thick, sticky secretions that obstruct passageways in the lungs and pancreas. Respiratory failure is the most dangerous consequence of cystic fibrosis. Secretions also block the pancreatic enzymes that help digest fats, proteins, and other nutrients, which can lead to malnutrition.

There is no cure for CF. Treatments for CF are aimed at relieving symptoms and minimizing complications. They can include digestive enzyme replacement for nutritional support, antibiotics to control infection, daily airway clearance therapy to help clear mucus from the lungs, and drugs to improve lung function. With early detection and lifelong comprehensive treatment plans, infants diagnosed with CF can be expected to live longer and in a better state of health than in the past. However, the debate continues as to the overall benefits of newborn screening for CF given the lack of a curative treatment regimen.

Burden of Disease

Cystic fibrosis is a serious genetic disease affecting approximately 30,000 people in the United States.[3] In 2004 there were approximately 23,000 patients in the Cystic Fibrosis Foundation's Patient Registry, of which 274 were from Connecticut.[4] CF occurs in approximately 1 in 4,000 births in the United States estimated from screening 1.5 million newborns during the past 10 years.[5] In Connecticut, the incidence appears to be comparable. Cystic fibrosis occurs in approximately 1 in 4,100 births based on screening 244,000 newborns from 1993 to 2004 at the University of Connecticut Health Center (D. Trebisacci; CT DPH, personal communication). In Connecticut newborns, CF is more common than PKU (1:11,000) and galactosemia (1:51,000) and less common than hypothyroidism (1:4,000) and sickle cell disease (1:2,000).[6]

Cystic fibrosis is much more common in Caucasians than in other populations. On the basis of data from U.S. newborn screening programs, birth prevalence is 1:2,500 – 3,500 births

♦ A carrier is an individual who possesses ("carries") a gene for a trait (e.g., CF), but who is not clinically affected by the condition.

among non-Hispanic whites, 1:4,000 – 10,000 births among Hispanics, and 1:15,000 – 20,000 births among non-Hispanic blacks. Connecticut-specific data are not available. Because of the different frequencies of mutations among various ethnic groups, the detection rate of DNA mutation testing is highly dependent on racial and ethnic background.

Although the majority of children are identified during the first year of life, individuals with milder symptoms may not be diagnosed until they are adults. Symptoms vary from person to person due, in part, to the more than 1,500 mutations of the CF gene. Nearly 10 percent of newly diagnosed cases in the United States are adults. There is no cure, but advances have been made in the treatment of CF, resulting in an increasing number of adults living with CF. Adults aged 18 and older compose nearly 40 percent of the CF population. The median age of survival has steadily increased from 25 years of age during the 1980's to 35 years of age in 2004.[4]

Current Status of Newborn Screening for Cystic Fibrosis in the United States

Screening panels and administrative structures differ among newborn screening programs in the 50 states. Geographic location determines the disorders for which newborns are screened, including cystic fibrosis. According to the July 14, 2006 U.S. National Newborn Screening Status Report, screening for cystic fibrosis is universally required by law in 19 states,[7] up from 14 just 3 months ago. In addition, CF screening is required but not yet implemented in 6 states, is universally offered but not required in 2 states, is offered to select populations in 3 states, and is not required in the remaining 20 states (Table 1).

Table 1. Status of Newborn Screening for Cystic Fibrosis in the U.S.

STATES	STATUS OF NEWBORN SCREENING FOR CYSTIC FIBROSIS
Colorado, Delaware, Iowa, Kentucky, Maryland, Minnesota, Mississippi, Nebraska, New Hampshire, New Jersey, New York, North Dakota, Oklahoma, Rhode Island, South Carolina, Virginia, Washington, Wisconsin, Wyoming	Universally required by law
Arizona, California, Florida, Missouri, New Mexico, Ohio	Required but not yet implemented
Massachusetts, South Dakota	Universally offered, but not yet required
Connecticut, Montana, Pennsylvania	Offered to select populations
Other 20 states	Not required nor piloted

There are 35 state health departments with NBS laboratories (including Connecticut). The other 15 states have contractual arrangements with other state health departments, university medical centers, private pathology laboratories, or commercial laboratories that specialize in NBS tests.

Current Status of Newborn Screening for Cystic Fibrosis in Connecticut

Not only do disparities exist nationally for CF newborn screening, but they also exist within the state of Connecticut. Screening for CF in Connecticut is not mandated as part of the newborn screening panel administered by the DPH, yet 20 of 29 birth hospitals in Connecticut offer CF testing. Approximately 30,000 out of 43,000 newborns (70%) annually are offered CF testing, leaving 30% who are not tested. The University of Connecticut Health Center (UCHC) does testing for 18 of the hospitals, while Yale University School of Medicine conducts tests for two other hospitals.

Different screening protocols are followed by the two testing centers, but once diagnosis is confirmed, newborns are referred for treatment at specialized CF care centers located at the Connecticut Children's Medical Center or Yale University School of Medicine, which are accredited by the Cystic Fibrosis Foundation.

CF testing programs have been in place for over 10 years at both UCHC and Yale. Mandating CF screening in Connecticut would most likely shift testing services from UCHC and Yale to the State Laboratory and would fiscally impact these facilities.

Screening Protocols

CF screening protocols vary by state. CF screening is not a diagnostic test and will not detect 100% of affected individuals. The initial screening test in all programs measures immunoreactive trypsinogen (IRT) in dried blood spots collected within 48 hours of birth. Infants with elevated IRT levels are referred for further testing. Various values are used to determine whether IRT is sufficiently elevated to necessitate further testing. Programs establish their own cutoff levels -- either a specified amount or a certain top percentile of the test batch.

Most testing involves two-tier protocols – either IRT/IRT or IRT/DNA screening (Table 2). The IRT/IRT protocol involves a second IRT determination at 2-3 weeks of age on a repeat blood specimen. At this age, elevated IRT levels are more specific for CF because IRT values decrease with age in infants without CF. If the second IRT is sufficiently elevated, then the infant is referred for diagnostic sweat testing. A single IRT test, or the IRT/IRT combination, is 85% to 90% sensitive and is associated with a relatively large number of false-positive results.[8]

Table 2.

METHODS USED FOR CF NEWBORN SCREENING

Testing method	Description	Follow-up sweat testing
IRT*/IRT	IRT analysis of the initial specimen obtained at 24-72 hours of life plus repeat analysis on a routine recall specimen	Required
IRT/DNA (ΔF508)	IRT analysis of the initial specimen, with positive specimens subsequently tested for the ΔF508 mutation	May not be required
IRT/DNA (multi-mutation panel)	IRT analysis of the initial specimen, with positive specimens subsequently tested for a panel of common mutations	May not be required

* IRT refers to the immunoreactive trypsin test, a blood test for elevated levels of trypsinogen

Persons with CF have mutations in the gene encoding the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. Although more than 1,500 mutations on the CFTR gene have been identified, the vast majority occur at a frequency of less than 0.1% in the affected population.[9] The most common mutation, ΔF508, appears in approximately 90% of the CF cases in the United States.[5] The IRT/DNA protocol involves second-tier DNA analysis of the CFTR gene with panels ranging from one (ΔF508) to 25 or more mutations. Utilization of multi-mutation panels has been increasing as the cost decreases. In Massachusetts, use of multiple-CFTR-mutation testing has been shown to increase sensitivity and postscreening prediction of CF over newborn screening algorithms that incorporate single-mutation testing.[10] Likewise, use of IRT/25 CFTR multi-mutation assays in Wisconsin has been performed with an estimated sensitivity rate of 99%, a substantial improvement over IRT testing alone, with 87% detection sensitivity and IRT/ΔF508 with 94% detection sensitivity.[11] Detection specificity is 99% regardless of the type of testing performed.

However, no consensus exists as to the best multi-mutation screening panel to use because the frequency distribution of CFTR mutations varies across racial and ethnic groups. To best serve heterogeneous populations, ethnic-specific mutations should be included in mutation screening panels.[12]

Differences also exist among program algorithms regarding the use of follow-up sweat-testing. Because certain analytic methods can falsely appear to be homozygous for CF mutations when, in fact, the patient is heterozygous for a normal allele and a CF allele,[13] sweat-testing should be used to confirm the diagnosis, recognizing that CF is a clinical diagnosis and not a genetic or physiologic one.[14] Sweat-testing can also provide a safeguard against clerical or laboratory errors that may have occurred, such as newborn blood spots that may have been switched. Sweat chloride concentrations are also used to distinguish classic/typical CF from non-classic/atypical CF patients.

CF mutation panels are commercially available that include the 23 mutations recommended for CF *carrier* screening by the American College of Medical Genetics (ACMG) in 2004. The ACMG had previously (2001) recommended a 25-mutation panel, but a subsequent review found two mutations to no longer meet the prior standard of 0.1% frequency in CF patients.[15] Whether this mutation panel is suitable for newborn screening is uncertain. A more appropriate NBS panel might be possible based on an analysis of severe mutations found in newborns with consideration given to racial/ethnic variations in populations of interest.[5]

Regardless of the number of mutations included in a screening panel, the number of mutations for which testing occurs will be deficient. Some cases may thus test falsely as negatives should they have mutations for which testing does not occur. Therefore, IRT/DNA algorithms need to include a "failsafe" protocol that identifies infants as being at risk for CF when they are found to have a highly elevated IRT value but no identified mutation.

Newborn screening for CF is being implemented in varying ways with different sensitivities. There is no consensus as to the best screening protocol. Because different populations have different mutation frequencies, the sensitivity of a given DNA mutation panel for detecting persons with CF varies by race and ethnicity. Therefore, technical issues such as which and how many mutations ought to be analyzed may affect how well implementation occurs.

Clinical Significance of Mutations

The genetic composition of an individual with CF does not account for the clinical variability seen in CF patients. There is a broad spectrum of CF phenotypes (i.e., physical, clinical, or biological characteristics of the disease in an individual) from classic CF to milder forms of the disease. The association between CFTR genotype (i.e., genetic constitution of an individual) and CF phenotype is variable. The highest degree of correlation between CFTR genotype and CF phenotype is observed for pancreatic function, and the lowest for lung function.[16] Patients with the common ΔF508 mutation frequently have severe pancreatic exocrine insufficiency, but they can have widely variable measurements of lung function ranging from normal to severe dysfunction.[17]

The poor correlation between CFTR genotype and severity and age of onset of lung disease suggests that environmental and secondary genetic factors (CF modifier genes) may play a role. Environmental factors that may affect the severity of lung disease include air pollution, smoking, bacterial infection, malnutrition, and certain therapeutic agents.[17] Candidate 'modifier' genes that may contribute to variation in lung disease include inflammatory and anti-inflammatory mediators, antioxidants, molecules involved in CFTR trafficking, and mediators of airway reactivity.[18]

It has become clear that CFTR genotype alone does not account for the clinical variability seen in CF patients, so positive genetic testing results may not indicate the severity and course of the disease in a patient. Factors, independent of CFTR, appear to influence CF outcomes, particularly lung disease, which is the primary cause of mortality in CF patients.

Benefits

The rationale for newborn screening is that early detection, rapid referral to an accredited CF center, and proactive treatment can improve outcomes for children with CF. The most compelling evidence of improved health outcomes has to do with nutrition and growth. Studies have shown that newborns identified with CF through newborn screening and who receive early treatment, have improved nutritional status, growth, and physical development, which, in turn, aids in the prevention of abnormalities in cognitive function.

The pulmonary benefits of CF newborn screening are less definitive because of the inconsistency in severity and age of onset of lung disease, the difficulty in measuring lung disease in children, and variations in genotypic and environmental factors. Although CF neonatal screening provides a potential opportunity for better pulmonary outcomes, it appears that other factors, such as respiratory infections and pancreatic status, significantly impact pulmonary prognosis.[19] Observational studies, however, provide indirect evidence that diagnosis by means of NBS may improve pulmonary health and survival of patients with CF.[20]

Screening may decrease the number of medical visits and the emotional stress on a family during the process of obtaining a clinical diagnosis. Infants who receive a diagnosis on the basis of clinical symptoms rather than screening usually experience a series of diagnostic tests and treatments before a conclusive diagnosis of CF is made. During this time families may experience anxiety, frustration, and emotional trauma because they don't know what is wrong with their child. Early diagnosis of infants with two mutations associated with CF through newborn screening may help to alleviate some of this parental anxiety. However, finding out that a child has CF usually causes parental stress, no matter when or how the diagnosis is established.[21] Psychosocial effects are more controversial for the larger number of families whose child is found to be a carrier of a CFTR-gene mutation. Genetic counseling is important

for providing educational and emotional support to families with a CF child or a CF-carrier child.

Another psychosocial benefit is related to the parents' newfound awareness of their own CF mutations and the opportunity it provides them for making informed future reproductive decisions. Genetic counseling is an important resource for assisting parents in making subsequent family planning decisions.

Risks

Potential harms from NBS include parental anxiety associated with a child testing false-positive, misunderstanding of carrier status, and unnecessary or even harmful therapies administered to children who are incorrectly identified with a disease or to children with mild or asymptomatic disease.

An adverse impact of screening relates to short-term psychological risks, namely the parental stress associated with a child falsely testing as positive. Confirmatory testing should be performed to reduce such false-positive results when a mutation is identified.[22]

Another risk associated with CF genetic testing is that cases will falsely be identified as negative when an infant's CFTR mutation is not included in the screening panel, leading to a false sense of reassurance. This risk points to the need for a failsafe provision for referral for sweat testing to detect affected infants with rare mutations, but who have elevated IRT values in the initial IRT screening test.

Newborn carrier identification is an unintended consequence of genetic testing, not seen in programs that use biochemical or physiologic testing. Information is often misunderstood regarding carrier status, causing parents to feel anxiety. Some families believe that being a carrier can cause illness.[23] Others think that their child will subsequently be inflicted with CF.

The risks of presymptomatic diagnosis relative to the respiratory system relate primarily to the overly aggressive or inappropriate treatment with antibiotics in efforts to preserve pulmonary function. Early introduction to antibiotics may lead to increasing antimicrobial resistance and premature acquisition of drug-resistant infections. This pulmonary risk, though, is not related to screening per se, but is a secondary consequence associated with medical management.

Concern also exists with the increasing frequency of CF patient-to-patient transmission of pathogens that occur at CF treatment centers. Vulnerable infants detected with CF by newborn screening may be exposed to older children with CF who have active lung infections,

leading to early acquisition of infections that are difficult to treat. Strict infection control policies at CF centers are recommended to prevent transmission of infectious agents.[24]

Studies suggest that genetic counseling plays a key role in the success of newborn screening for CF. Those who receive appropriate genetic counseling tend to better understand the implications of genetic data.[23] Counseling also helps with emotion management and decision-making for parents. Demand for genetic counselors is expected to increase as genetic testing evolves. There appears to be an inequitable geographic distribution of genetic counselors in Connecticut -- one third of the state's 39 certified counselors are located in Fairfield County and they serve only 19% of the state's population.[6]

In addition, both the general public and community health providers need to be better informed about the implications of all newborn screening results. DPH will need additional resources to provide educational materials to address this need.

Costs of Screening and Diagnosis

When comparing costs of newborn screening and diagnosis for CF with that of the traditional method of diagnosis for CF involving sweat tests performed because of symptoms of the disease or a family history, the former may be a cost-saving alternative due primarily to the savings associated with a decreased number of sweat chloride tests required.[25] Because fewer sweat tests are required compared with the traditional method of diagnosis, a CF NBS program is a potential cost-saving alternative to clinical diagnosis alone. However, because approximately 70% of newborns are already being screened for CF in Connecticut, much of the potential cost-savings are most likely already built into the system. That is, the number of sweat chloride tests being performed in Connecticut has already been reduced with the use of newborn screening performed at UCHC and Yale University School of Medicine.

The laboratory cost of newborn screening varies with the screening algorithm. Data from the Wisconsin screening program indicate that the laboratory cost of IRT screening is $1.50/test, the cost of a single-mutation (ΔF508) analysis is $20.50, and the cost of a multiple-mutation test is $50.70 as reported by Rosenberg et al.[27] Using the methodology and costs per test ascertained by Rosenberg et al., costs of CF laboratory newborn screening and diagnosis in Connecticut were estimated (Table 3). Data published by the Connecticut Department of Public Health show 43,511 births by occurrence in 2003.[26] The incidence of CF has been estimated as 1 in 4,100 births as described previously. As in Wisconsin, it is assumed that the same percentage of IRT tests are referred for DNA testing (infants with IRT levels above the 96th percentile). Therefore, the estimated annual cost of the IRT/DNA test is $153,485. The estimated total sweat test cost associated with screening follow-up is $16,301, assuming the

Table 3.

Estimated Costs of CF Laboratory Screening and Diagnosis in Connecticut, 2003*

	Count	Cost ($) per test	Total cost ($)
IRT			
All births by occurrence, 2003	43,511	1.50	65,266.50
CFTR multi-mutation panel			
Top 4%	1,740	50.70	88,218.00
Sweat test	101	161.40	16,301.40
Total Cost			169,785.90
No./Cost per diagnosed CF	11		15,435.08
Cost per birth for IRT/DNA test			3.53
Cost per birth for screening & diagnosis			3.90

* Estimates for cost per test as well as number of tests from Rosenberg et al.[27] based on data from Wisconsin State Laboratory of Hygiene.

Number of births from CT Department of Public Health, Planning Branch, Health Care Quality, Statistics, Analysis, and Reporting Unit.

Number of CF diagnosed based on estimated annual CT incidence of 1 in 4,100.

same percentage of those having a sweat test from the IRT screen as in Wisconsin (approximately 5.8%). The estimated total cost of CF newborn screening and diagnosis in Connecticut is $169,786, which is equivalent to $3.90 per screened baby or approximately $15,400 per newly diagnosed newborn with CF. The results for Connecticut are comparable to the laboratory costs of CF newborn screening in Wisconsin -- $3.55 per baby for the IRT/multi-mutation screen and $4.00 including the follow-up sweat test.[11]

Based on information provided by states to a U.S. General Accounting Office survey, Connecticut reported that in state fiscal year 2001, the State spent $39.20 for each infant screened.[28] Expenditures support laboratory activities such as processing and analyzing specimens, and evaluating the quality of laboratory activities. They also support program administration/follow-up expenditures such as notifying appropriate parties of test results, confirming that infants received additional laboratory testing, confirming that infants diagnosed with disorders received treatment, and providing education to parents and health care providers. This emphasizes the fact that newborn screening is a comprehensive integrated system with costs that go well beyond that of an inexpensive laboratory test. Costs of implementing newborn screening for CF, therefore, require additional information on the costs of follow-up, genetic counseling, and providing care.

Connecticut charges a $28 newborn screening fee, which is not sufficient to cover the State's expenditures for the program. Even if the fees were enough, they are not directly used to support newborn screening. Instead they are deposited into the State's General Fund, forcing the newborn screening program to compete for limited state resources. States like California

use a fee-based approach to fund newborn screening whereby fees collected go directly into a genetic disease testing fund and are used to support comprehensive screening services. This raises the policy issue of whether mandated screening should be financed from tax revenues or from a fee. Regardless of the approach taken, additional state resources are needed to provide expanded services.

Because the University of Connecticut Health Center (UCHC) and the Yale University School of Medicine currently offer newborn screening programs for cystic fibrosis in Connecticut, shifting the responsibility to the Department of Public Health would fiscally impact these facilities, particularly UCHC. In addition, trained personnel may lose their jobs.

The DPH would require additional personnel and equipment both at the Laboratory for testing and in the Newborn Screening Program for testing follow-up and educational activities. During the 2006 legislative session when Senate Bill 162: An Act Requiring Newborn Infant Health Screening for Cystic Fibrosis was proposed, the Office of Fiscal Analysis estimated that DPH would incur costs of approximately $350,000 annually to implement the bill. It was also estimated that an additional $200,000 would be needed to support diagnostic testing, genetic counseling, and medical treatment activities at the two CF-accredited treatment centers in the State.

Carrier Status

A by-product of newborn screening for CF using a genetic testing protocol is carrier identification. Screening by DNA mutation analysis for CF may inadvertently identify newborns who are not affected by the condition, but who carry a gene for CF and are at risk of having a future child with CF should they procreate with another carrier. Many more carriers can be identified through screening than CF cases. Although not the intent of screening, information has been gained that can affect the child's future reproductive choices. Knowledge of newborn carrier status, as well as CF-affected status, also has implications for other family members. Parents and other family members may also be identified as carriers through genetic testing, thus affecting future reproductive choices.

The information that a child is a carrier, implying that at least one of the parents is also a carrier and at increased risk of having a CF-affected child, is not easily conveyed. Because the intent of newborn screening for CF is early detection of infants *with* the condition and not carrier detection, guidance is needed regarding communication policies for carrier status.

Conclusion

Advances in nutrition, earlier diagnosis, newer antimicrobial and anti-infective therapy, and advances in critical care have transformed cystic fibrosis from a disease characterized by death in early childhood to a chronic illness, with most patients living to adulthood. But despite this progress, there still is no cure for the disease and most patients eventually succumb to infections of the airways and lung failure.

Nevertheless, medical advances along with social and political forces are pushing state newborn screening programs to include testing for cystic fibrosis. Not only do disparities exist nationally for CF newborn screening, but they also exist within the state of Connecticut -- 20 of 29 of the State's birth hospitals offer CF testing on a voluntary basis. The challenge remains for the Connecticut Department of Public Health to respond to these influences in a deliberate manner that recognizes the many issues involved.

The evidence favoring CF newborn screening continues to grow. Advocates point to the benefits for CF screening --- reductions in mortality, improved nutrition and cognitive function, informed reproductive decisions, and the potential for improved pulmonary function. Screening may also decrease the number of medical visits and the emotional stress on a family during the process of obtaining a clinical diagnosis. The CDC believes that newborn screening for CF is justified "on the basis of moderate benefit and low risk of harm."

With the emphasis shifting from "Should we screen?" to "How should we screen?",[29] it is important to recognize that genetic testing for cystic fibrosis involves more than just a simple laboratory test. More than 1,500 mutations on the CFTR gene have been identified, laboratory screening protocols vary, and follow-up tracking and treatment services need to be available along with genetic counseling. Optimal outcomes will only occur in a system that provides effective communication between health professionals and families, appropriate genetic counseling, and proper medical care.

Because the detection rate of DNA mutation testing is highly dependent on racial and ethnic backgrounds, decisions regarding which and how many mutations to test for remain controversial. In 2001 the American College of Medical Genetics had recommended a 25-mutation panel for carrier testing. By 2004 they had already eliminated two mutations from the panel. There has not been a separate mutation-panel recommended for newborn screening. On May 9, 2005 the FDA approved the first DNA-based test to detect cystic fibrosis.[30] The Tag-It 40+4 test can detect 40 mutations and 4 variants, including the 23 mutations recommended by the ACMG. Testing for even 40 mutations will result in some false-negatives for which a failsafe protocol must be in place.

Compounding this problem is the fact that disease symptoms do not correlate well with genotypic results. Studies have shown that CFTR genotype alone does not account for the clinical variability seen in patients with CF, so positive genetic testing results may not indicate the severity and course of the disease in a patient. Environmental and secondary genetic factors, independent of CFTR, appear to influence CF outcomes. As such, treatment of presymptomatic patients must be carefully managed.

As government-mandated screening expands, the issue remains as to whether screening should be financed from tax revenues or from fees. Although fees are assessed in Connecticut, they are absorbed into the State's General Fund and not necessarily appropriated to support the newborn screening program. Even so, the fees collected fall short of the expenditures incurred per newborn infant.

Sources of funding need to be identified for each newborn screening system component, including follow-up, diagnosis, treatment, and education of parents and health care providers. "States should not mandate [expanded] screening before a comprehensive program is in place to assure appropriate follow-up and treatment."[31] Parts of the "system" are already in place in Connecticut with the CF-testing and treatment centers that currently exist. Shifting responsibility away from the testing facilities to the DPH will fiscally impact these programs. Staffing requirements will also be affected and need to be addressed.

Screening by DNA mutation analysis for CF will inadvertently identify newborns who are not affected by the condition, but who carry a gene for CF. Guidance is needed regarding communication policies for carrier status.

Before universal newborn screening for cystic fibrosis is legislatively mandated in Connecticut, careful consideration should be given to the issues and implications involved in the "brave new world" of DNA testing.

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