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Appropriateness of Newborn Screening for α1-Antitrypsin Deficiency

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ABSTRACT

Objective: The Alpha-1 Foundation convened a workshop to consider the appropriateness of newborn screening for α-1-antitrypsin (AAT) deficiency.
Methods: A review of natural history and technical data was conducted.
Results: Homozygous ZZ AAT deficiency is a common genetic disease occurring in 1 in 2000 to 3500 births; however, it is underrecognized and most patients are undiagnosed. AAT deficiency can cause chronic liver disease, cirrhosis, and liver failure in children and adults, and lung disease in adults. The clinical course is highly variable. Some neonates present with cholestatic hepatitis and some children require liver transplantation, but many patients remain well into adulthood. Some adults develop emphysema. There is no treatment for AAT liver disease, other than supportive care and liver transplant. There are no data on the effect of early diagnosis on liver disease. Avoidance of smoking is of proven benefit to reduce future lung disease, as is protein replacement therapy. Justifying newborn screening with the aim of reducing smoking and reducing adult lung disease-years in the future would be a significant paradigm shift for the screening field. Recent passage of the Genetic Information Nondiscrimination Act (GINA) and the Affordable Care Act may have a major effect on reducing the psychosocial and financial risks of newborn screening because many asymptomatic children would be identified. Data on the risk–benefit ratio of screening in the new legal climate are lacking.
Conclusions: Workshop participants recommended a series of pilot studies focused on generating new data on the risks and benefits of newborn screening.

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α-1-Antitrypsin (AAT) deficiency is a metabolic-genetic disease that, in its classical and most typical form, is caused by homozygosity for the AAT mutant Z gene (*SERPINA1*). These individuals, so-called ZZ or ''PIZZ'' in World Health Organization nomenclature, occur in 1 in 2000 to 3500 births in North American and European populations. AAT deficiency is one of the most common single-gene diseases in the United States, with approximately 100,000 individuals affected, although it is widely underrecognized and most patients are undiagnosed (1–3). There is no newborn screening for AAT deficiency, nor is there any other organized or widely accepted patient identification process outside of pilot screening studies and the testing of symptomatic individuals in the context of routine medical care. This is in spite of the fact that symptomatic infants with AAT deficiency are more common than infants affected by many other conditions already represented on the expanded newborn screen. These considerations have led to an analysis of the indications for instituting newborn screening for ZZ AAT deficiency. Extensive documentation of the genetics, gene frequency, natural history, and biochemistry of AAT is found in the monograph Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency and the other references noted, although we briefly review the disease's natural history, technical data, and rationale for newborn screening as discussed by the workshop participants (1,2).

AAT is a protein produced in large amounts in the liver and then secreted into serum. Its physiologic function is to inhibit neutrophil proteases when these enzymes leak from leukocytes into extracellular fluid during inflammation (1). In this way, AAT is critical in protecting host tissues, especially the elastic fibers of the lung, from nonspecific damage during infection and inflammation. The Z mutant of the *AAT* gene encodes the synthesis of a mutant protein, which is retained and accumulates in the liver rather than being appropriately secreted into serum. Accumulation of the Z mutant AAT protein in the liver can cause chronic liver disease, including cirrhosis and liver failure, in infants, children, and adults, whereas the decreased circulating levels of AAT significantly increase the risk of emphysematous lung disease in adults (4,5). Individuals heterozygous for 1 normal M allele and 1 disease Z allele, so-called MZ, are generally considered asymptomatic carriers, although some data indicate a possible small increase in risk for some lung and liver conditions (1,6,7).

The natural history of ZZ AAT deficiency is highly variable (1). Studies indicate that approximately 20% of homozygous ZZ newborns develop symptomatic cholestatic hepatitis, although as

many as 50% of ZZ infants and children are likely to have some kind of hepatic abnormality, including elevated enzymes, hepatomegaly, or nutritional problems, at some point during childhood (8). The risk of life-threatening liver disease in childhood (liver failure leading to death or transplant) is approximately 5%, according to the only unbiased cohort identified in a newborn screening study undertaken in Sweden in the 1970s (1,2,8–11); however, it is unclear whether the results from this genetically homogeneous Swedish population are fully applicable to a population such as North America with a different and likely wider array of modifier genes. This is because there are a number of presentations and complications of liver disease reported from various single-center studies that are not represented in the Swedish newborn cohort (12–14). Despite incomplete data and a lack of exact numbers, it was shown in the Swedish study and in limited US screening that a significant proportion of ZZ children, likely the majority, are asymptomatic and are unlikely to develop any severe disease until adulthood (13). Autopsy studies in adults suggest that the lifetime risk of cirrhosis may be as high as 50% and appears to increase in incidence in late adulthood (15). The risk of hepatocellular carcinoma is increased in ZZ patients, although the magnitude of the risk is unclear. ZZ children may experience asthma or recurrent infections, although emphysematous lung disease does not develop until early or middle adulthood (1,16,17). The lifetime risk of serious lung disease may be 50%, but is dramatically increased by personal smoking and secondhand cigarette smoke exposure. Presently, there are no specific treatments available for ATT-deficiency liver disease, other than standard supportive therapy for liver failure and liver transplantation. Intravenous protein replacement with human plasma–derived AAT has been used for >20 years as a US Food and Drug Administration–approved treatment for the associated lung disease in adults, but it has no effect on the progression of liver disease.

Only testing of targeted populations and not newborn screening is used for the detection of AAT deficiency (9). Patients with obstructive airway diseases, liver disease of unknown etiology, or therapy-resistant asthma are considered candidates for testing as recommended in a consensus statement of the European Respiratory Society, the American Thoracic Society, and the World Health Organization (WHO) (1,2). The statement recommends that all individuals with chronic obstructive pulmonary disease be tested for AAT deficiency. The rationale for this recommendation, even in older adults, is that it could identify carriers who may have at-risk family members. In addition, adults with incompletely reversible asthma, unexplained bronchiectasis, and unexplained liver disease, as well as individuals who are relatives of known affected patients should be tested.

More than 100 other mutations in the *AAT* gene have been identified, but the Z mutant is associated with the vast majority of disease (1). Some patients carry the rare *null/null* and *Z/null* genes, which are associated with adult emphysema, but these individuals do not develop liver disease. The only other mutation reviewed was the S mutant. This is a mutation thought to be equally as common as Z, but not associated with disease as is MS or SS; however, some SZ individuals may develop emphysema and some SZ individuals have been described to have liver disease. The risk of disease in SZ is thought to be considerably lower than ZZ for both lung and liver. A total of 54 SZ individuals were identified in the Swedish cohort, but none has ever developed liver disease. After review of these data, the workshop participants focused recommendations on ZZ homozygous individuals, unless or until new data on other genotypes become available.

Significant changes have occurred in recent years in the US legal environment for individuals with genetic disease. The Genetic Information Nondiscrimination Act (GINA) bill was passed by Congress in 2008 and took effect in 2009. It protects individuals from discrimination in health care by prohibiting health insurance providers from requiring genetic information, or the genetic information of a family member, for eligibility, coverage, underwriting, or premium-setting decisions. It also prohibits health insurance providers from using genetic information to collect with intent to make enrollment or coverage decisions or requiring that an individual or an individual's family member undergo a genetic test. If genetic information is acquired during research, then it may not be used for underwriting purposes; however, GINA does not apply to members of the US military, veterans participating in Department of Veterans Affairs programs, small companies with fewer than 15 employees, or the Indian Health Service. GINA also does not include protections from genetic discrimination in life insurance, disability insurance, or long-term-care insurance. GINA covers only an individual's predictive, presymptomatic, genetic information, and does not cover an individual if he or she has been diagnosed or shows clinical signs of a particular condition. Another major change in the medicolegal environment is the Affordable Care Act. This removes denials of coverage for a preexisting condition, but still allows variable rates to apply based on health status. The Affordable Care Act also has no effect on life insurance denials. Other changes may follow. Understanding how these new laws influence the risk–benefit ratio of newborn screening will be a major focus of future pilot studies in the United States.

METHODS AND MEETING OBJECTIVES

The Alpha-1 Foundation convened a focused workshop in Washington, DC, to investigate the risks, benefits, costs, and feasibility of newborn screening for AAT deficiency. The workshop was led by co-chairs David Mannino, MD, R. Rodney Howell, MD, and Richard Sharp, PhD, and included physicians, scientists, representatives of health advocacy groups, federal employees, patients, and patients' families. Face-to-face meetings took place September 17 to 18, 2008; manuscript recommendations and impact of the Affordable Care Act were reviewed in June 2010; final assessment of recommendations with implementation of the Affordable Care Act was made in December 2011 and June 2012, and the final manuscript editing was performed in June 2013. This workshop was a follow-up to a 1999 screening and detection workshop, which recommended that screening for AAT deficiency should be limited to at-risk populations, such as patients with established liver disease, families with a positive history, and patients with chronic obstructive pulmonary disease, and should not progress to newborn screening. In part, the conservative screening recommendations produced by the previous workshop resulted from concerns about genetic discrimination and other unintended consequences of identifying asymptomatic and healthy patients with AAT deficiency. The recent passage of the GINA has lessened many of these concerns, suggesting a need to revisit the pros and cons of newborn testing for AAT deficiency. The increased protections to individuals with preexisting conditions in the Affordable Care Act further support this reassessment. During the 2-day workshop, experts from multiple government organizations and academia, as well as health care providers, patients, and patient advocacy groups, discussed relevant issues. The topics explored were as follows: Is there a sufficient scientific rationale for newborn screening for AAT deficiency to justify any possible negative consequences and to address cost issues (1,2,9–11)? What steps are necessary to add a condition to the newborn screening panels of individual states? What public health infrastructure exists to accommodate the possible influx of newly diagnosed patients and carriers and what would be needed to build proper follow-up and educational programs? What advocacy efforts would be required to convince states to add AAT deficiency to their newborn screening panels? Does the required technology exist to implement newborn screening for AAT deficiency?

WORKSHOP RESULTS

Is There a Sufficient Scientific Rationale for Newborn Screening for AAT Deficiency?

It was determined by the workshop participants, after extensive review of the available literature, that there is insufficient knowledge of the risk–benefit ratio of newborn testing for this disease at this time (3,9–11). There is no specific treatment for AAT deficiency liver disease, which is the primary source of morbidity and mortality in children, other than liver transplant. It is not clear whether improved general care provided earlier in life, which may be 1 result of presymptomatic detection of many ZZ patients, would result in reduced morbidity from liver disease or reduced transplantation. Avoidance of smoking has clear benefits to these patients, but those benefits are decades in the future for an individual diagnosed at birth. There is no disease detected by newborn screening in which the benefits are so distant in time. A single study of a cohort of patients identified at birth in Sweden in the 1970s suggested a greatly reduced rate of smoking in adulthood by individuals identified at birth, although these data have not been reproduced in other populations (10). Studies in this same Swedish cohort also found significant increases in psychosocial stress in the families of the patients, even when these patients were asymptomatic and healthy throughout childhood. In the United States, there have been significant risks of psychosocial stress negative consequences for the detection of asymptomatic individuals with any disease because of concerns for loss of health insurance, loss of employment, and other negative financial and social outcomes; however, the increased access to care for individuals with preexisting conditions, which are promised in the Affordable Care Act, are likely to have a major impact on these considerations. The combination of GINA and the Affordable Care Act, although advantageous when considering many aspects of medical care, still leave both presymptomatic and symptomatic genetic disease communities vulnerable to reduced access to life insurance, long-term care insurance, and other options available to undiagnosed people. It was recommended that pilot studies be conducted to determine whether early detection improves outcomes and what psychosocial risks may result (see specific recommendations below). Possible themes for pilot studies could include defining the risk–benefit ratio, and analyzing the psychosocial and financial costs of early detection in this new legal environment. A pilot study in different age cohorts could be done to analyze smoking prevention and parental smoking cessation correlating to prevention of lung disease (18). A pilot study analyzing liver disease management would also be beneficial, especially in children (1,3,19).

What Steps Are Necessary to Add a Condition to the Newborn Screening Panels of Individual States?

It was agreed that the Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) nomination is the most important first step in adding a condition to the screening panel. There are 3 nomination considerations. The first is the incidence and natural history of the condition in question. Presently, incidence data for ZZ AAT deficiency in North America are not certain but can be estimated to be 1 ZZ per 2000 to 3500 live births, which is similar to or greater than the incidence of cystic fibrosis and other conditions that are currently screened for (1). As noted above, the morbidity is highly variable and, with present knowledge, not predictable for an individual patient. Many ZZ individuals are asymptomatic in childhood.

The second consideration is cost; a cost-efficient test must be readily available. The panel's analysis suggests that a reliable test could be developed, with costs similar to other ongoing screening practices. Current analytical methodologies are already being studied for use on dried blood spots, and analysis by participants suggested that economies of scale would likely bring the cost to the range of $5 per test. The third consideration is treatment. There is no specific treatment for pediatric AAT-deficiency liver disease, other than supportive care and transplantation. Newborn testing may be a new paradigm, shifting the purpose from a pediatric medical treatment focus to an overall lifelong health, smoking-avoidance focus. The treatment plan would focus on the noninvasive, preventive intervention of smoking avoidance in the index patient and smoking cessation in household contacts. It is vital that the efficacy of these medical interventions be investigated and proven in North America. There must be specific, evidence-based follow-up plans and advice to parents on preventive methods.

What Public Health Infrastructure Exists to Accommodate the Possible Influx of Newly Diagnosed Patients and Carriers and What Would Be Needed to Build Proper Follow-up and Educational Programs?

Infrastructure does exist for care and follow-up of the conditions presently identified on state newborn screens. In many cases, these are the same centers that and clinicians who deal with pediatric AAT-deficiency liver disease; however, there are additional needs that must be addressed, such as what evidence-based advice and resources should be made available to a group of newly identified but asymptomatic patients and families. There are numerous community-based ATT deficiency support groups, at least $\geq$1 in each state. There are 53 clinical resource centers available in the United States, mostly based at academic medical centers, which regularly accept referrals for AAT patient evaluations. They could be expanded to include more pediatric support, although many already include a pediatric gastroenterologist. The majority of these community resources and centers have been organized privately by the Alpha-1 Foundation. Rosters of practitioners knowledgeable about and interested in AAT deficiency at these sites are kept and publicized. Biannual meetings of site representatives are organized by the Foundation, but no direct financial support is given to the centers. It is unclear whether this loose infrastructure is adequate for an influx of newly diagnosed infants. For the infrastructure to be ready for α-1 newborn screening, obstetrics and gynecology practitioners, family practitioners, general pediatricians, nurse practitioners, physician assistants, genetic counselors, and other medical professionals who would commonly interact with newborns and their families would need more education to understand the screening results and to properly inform patients and families about the condition and the care of asymptomatic patients. Depending on the screening method used, many carriers may be identified and they would need to have a support system for education. The question would also arise as to the notification of carriers or of individuals with indications of low levels and rare genotypes. Regional or state-level clinical expertise needs to be developed for a standardized education plan to be implemented upon diagnosis. The potential benefits of carrier detection would be possible mitigation of the small risk of lung and liver symptoms that, some data suggest, is associated with the carrier state, as well as general reproductive information to families; however, the risks of identifying up to 2% of the US population as carriers could lead to significant costs and psychosocial stress compared with the small number of individuals with health risks.

What Advocacy Efforts Would Be Required to Convince States to Add AAT Deficiency to Their Newborn Screening Panels?

It was agreed that the first step is to achieve the support of the SACHDNC, which will increase the chances that states adopt screening for AAT deficiency. Using the Newborn Screening Saves Lives Act, states will be eligible for grant funds once they adopt the recommendations of the SACHDNC. Partnerships with professional associations, such as the American Academy of Pediatrics, the Association of Public Health Laboratories, the Genetic Alliance, the March of Dimes, and the American College of Medical Genetics, would help with legislation support.

Does the Required Technology Exist to Implement Newborn Screening for AAT Deficiency?

It was determined that appropriate technology is available (see diagnostic discussion in reference (1)). It was decided that the objective of newborn screening would be to identify ZZ individuals only and not carriers (and not SZ individuals unless new pilot data becomes available) because the majority of morbidity and mortality involves ZZ homozygotes. Available practical methods include protein assays, tandem mass spectrometry, and DNA-based testing. The protein assay (enzyme-linked immunosorbent assay) is a good option because it does not detect carriers and is easily automated for high throughput; however, there are no normal levels known for newborns, and levels of AAT in serum can vary with illness and age. A well-controlled, population-based study of AAT levels in normal newborns would be a benefit to the field. Tandem mass spectrometry testing is available in laboratories, but it is not available specifically for AAT deficiency. DNA-based testing is inexpensive and both specific and sensitive. Conversely, it will detect carriers, but it will not detect null genotypes.

Taking into account recent legislative and technological developments, as well as medical advances in the science of ATT deficiency and the work performed by the Health and Human Services–appointed SACHDNC, workshop participants concluded that there is insufficient evidence to support expanded newborn screening for this disease at the present time; however, it was recognized that the certainty to develop a final recommendation would require new data that has not yet been collected. To develop the knowledge base required to assess the appropriateness of adding AAT deficiency to state newborn screening panels, workshop participants recommended that a number of pilot studies be undertaken. For example:

1. A pilot study to explore ethical issues related to newborn screening for AAT deficiency, such as best practices for informing families of test results, managing psychosocial and financial costs of early detection, returning ambiguous test results and information on carrier status, and questions of misattributed paternity
2. A pilot study to explore the following issues related to providing sufficient scientific rationale for newborn screening for AAT deficiency: whether early detection improves liver outcomes, defining risk–benefit ratio, smoking prevention and parental smoking cessation, and liver disease management
3. A pilot study to identify the best methodologies to implement a newborn testing program for AAT deficiency, to develop a family support system, and to determine the impact on pediatric liver care

Workshop participants also made the following general recommendations about the addition of AAT deficiency to state newborn screening panels:

1. Obtaining official SACHDNC nomination is a critical step in adding a new disease to any newborn screening panel.
2. Targeting SACHDNC for approval, partnerships should be pursued with other professional associations including but not limited to the American College of Medical Genetics.
3. Screening of newborn for AAT should be targeted to find only ZZ individuals and not carriers or SZ at the present time.
4. Testing program infrastructure should include expanded pediatric support in clinical resource centers, education on AAT deficiency for obstetrics and gynecology and other physicians, and development of regional or state-level clinical expertise for a standardized education plan.
5. Producing a decision model paper should determine the total lifetime cost of diagnosing 1 person with AAT deficiency.

WORKSHOP CONCLUSIONS

Given the demonstrated and perceived benefits and risks of newborn testing for ZZ AAT deficiency summarized in this article, the majority of the workshop participants concurred that the potential for newborn screening should be further explored with appropriate pilot studies. The Alpha-1 Foundation will define its role in implementing such studies, possibly in partnerships with other interested entities. It is understood that a newborn screening system needs to encompass not only testing but also a comprehensive approach by building the necessary infrastructure and educating health care providers and affected families. Recommending newborn screening for ZZ AAT deficiency, in the absence of a treatment for the associated pediatric liver disease but with the justification that early diagnosis would reduce smoking and adult lung disease, would be a significant paradigm shift for the field of newborn screening. The detection of a large number of individuals who would be asymptomatic and healthy throughout childhood was also a concern. Recent passage of the GINA and the Affordable Care Act may have a major impact on reducing the psychosocial consequences of newborn screening. Study of the impact of the new US legal environment on the results of newborn screening should be an intense area of focus. The findings summarized in this report are of interest to the broader AAT-deficiency disease community, to other rare disease organizations, and to government agencies responsible for implementing and regulating newborn screeningprograms.

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