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Newborn Screening Update

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Introduction

The Florida Newborn Screen began in 1965 as part of a nationwide public health initiative to identify genetic disorders at birth in which early intervention was shown to decrease morbidity and mortality. Currently, Florida screens for 54 disorders, 32 of which are considered core disorders recommended by the United States Department of Health and Human Services Recommended Uniform Screening Panel. The additional 22 secondary disorders were added between 2006 and 2012, per recommendation from the American College of Medical Genetics (ACMG). Between 2018 and 2020 four new conditions, X-Linked Adrenoleukodystrophy (X ALD), Pompe disease, Mucopolysaccharidosis Type 1 (MPS 1), and Spinal Muscular Atrophy (SMA), will be added for a total of 57 genetic disorders. The addition of these four complex disorders has posed new challenges in diagnosis, treatment, funding, and in educating the medical community.

A Brief History of the Newborn Screen

In the 1960s, Dr. Robert Guthrie, a National Institute of Child Health and Human Development researcher, developed the first mass-screening test for the metabolic disorder phenylketonuria (PKU)(Edwards, 2007). If left untreated, individuals with this condition develop severe intellectual disability, but when diagnosed in infancy, medical intervention can reduce or eliminate effects of the disorder. Since the onset of newborn screening, consensus on the inclusion criteria for additional disorders has followed a similar rationale to the original PKU test. Today, screening is performed on every baby in the United States that is born in a hospital or birthing center. A heel prick for a blood collection card is performed at 24-48 hours of life and sent to a state-run laboratory center for analysis. The ACMG provides ACT Sheets for each condition included on the newborn screen (NBS). Given the rarity of many of the conditions, these ACT Sheets help inform clinical decision making and provide physicians and families with information on the condition, diagnoses, and next steps. Currently, parents must opt-out of this test and can do so for any reason. A written refusal must be obtained and documented in the medical record.

How Disorders are Chosen for Screening

The number of screened disorders vary slightly from state to state, but generally require that: 1) the disorder can be identified between 24-48 hours after birth and would not normally be detected otherwise, 2) there is a reliable and timely test with both high sensitivity and specificity, 3) there is a proven medical intervention that can be implemented in a timely and effective manner and will positively impact health outcomes for the individual (Edwards, 2007). By April 2011, all states were screening for at least 29 conditions.

Florida's Newborn Screen Program

In Florida, each specimen arrives at the Bureau of Public Health Laboratories in Jacksonville, ideally with 24 hours of collection. All results are sent back to the hospital or birthing center and then forwarded to the baby's pediatrician. If the screening results for metabolic or genetic disorders are abnormal, designated Genetics Centers located in Gainesville, Tampa, and Miami, will contact the parent and/or physician about additional confirmatory testing and follow-up. Since early detection of these conditions can be live saving, it is important for families to confirm their correct contact information before leaving the hospital. Results are usually reported out seven days after the specimen arrives at the laboratory. When a baby is found to have an abnormal NBS, it is imperative for parents or guardians to follow the physician's instruction immediately to determine if treatment is needed.
The biggest expansion to Florida's program came in 2006 when 39 core and secondary disorders were added as technological advances in tandem mass spectrometry became readily available. Between 2006 and 2012 another five disorders were added, for a total of 53 core and secondary conditions. These disorders include inborn errors of metabolism, endocrine disorders, hemoglobin disorders, hearing loss, and other genetic conditions. Florida's list remained unchanged until 2018, when the Genetic and Newborn Screening Advisory Council added X-ALD to the panel. Three more conditions, SMA, Pompe disease, and MPS 1 will be added by August of 2020. These recent additions have added new funding, testing, and reimbursement challenges for the Florida medical community.

X-linked Adrenoleukodystrophy

X-ALD is a genetic condition that affects 1 in 17,000 individuals worldwide and was added to the Florida NBS in 2018. This condition is considered an X-linked recessive condition meaning it affects males more severely than females. There are three distinct types of the condition. In the most severe instances, symptoms typically appear between the ages of four and ten but can begin as early as two years old. Symptoms usually begin to show as attention deficit disorder, then progress to loss of intellectual function, vision and hearing loss, and motor deterioration. Life expectancy for the disorder is based on the severity of the signs and symptoms and how quickly the disorder progresses. The other two forms have a later age of onset and symptoms may not progress as rapidly. Currently, treatment involves hematopoietic stem cell transplantation (HSCT), corticosteroid replacement therapy, and medications to help relieve symptoms. HSCT is most effective if done in the early stages of the disease and has been proven to drastically slow the progression of leukodystrophy. The procedure does come with its own risks, and is not affective at treating adrenal insufficiency or other types of myelin and neural degradation (Kemper et al., 2017).

Pompe Disease

Pompe disease is an autosomal recessive lysosomal storage disorder that affects 1 in 40,000 individuals in the U.S. There are three different types of the condition, classic infantile-onset, non-classic infantile-onset, and late-onset. The infantile forms consist of the most severe symptoms, including progressive muscle weakness, heart defects, and serious breathing complications that lead to death in childhood if left untreated. The late-onset form may not become apparent until late childhood or adulthood and symptoms are usually milder and are less-likely to involve the heart. Treatment currently involves enzyme replacement therapy (ERT), physical and respiratory therapy, and dietary changes. ERT should begin as soon at the diagnosis is made as has been shown to increase respiratory and motor function. Patient with the condition will still need to be monitored closely for recurrent infections, respiratory and cardiac status, and musculoskeletal function (Leslie & Bailey, 2017).

Mucopolysaccharidosis Type 1

MPS1 is an autosomal recessive lysosomal storage disorder that affects 1 in 100,000 individuals. There are overlapping phenotypes of the three syndromes associated with this condition, but MPS1 can generally be divided into severe and attenuated types. The condition affects multiple organ systems and includes intellectual disability, vision loss, heart disease, and airway obstruction. Individuals with the attenuated type usually have a milder presentation of symptoms that do not progress as quickly and typically live into adulthood. Currently, treatment involves ERT, HSCT, physical therapy, surgery, dietary changes, and medications to relieve symptom burden. HSCT is the standard treatment for MPS1, though is does come with its own risk and is only recommended for children with severe MPS1. Treatment has been shown improve cardiac and respiratory function, slow cognitive decline in children with mild intellectual disability, and positively affect other organ systems. For patients with the attenuated type, ERT has been shown to improve growth, mobility, breathing, and liver size (Clarke, 2006).

Spinal Muscular Atrophy

SMA is an autosomal recessive condition that affects 1 in 8,000-10,000 people worldwide. There are four different types of SMA that range in severity and age of onset. The condition results in atrophy of skeletal muscles due to deterioration of motor neurons that control muscle movements. In rare cases, the disorder can present prenatally, and these individuals do not survive past infancy. The most common type is SMA1. Muscle weakness is present at birth or within the first few months of life. Children with this type do not usually survive past childhood due to respiratory failure (Prior & Finanger, 2016). Treatment for SMA is evolving quickly. In 2016 the Food and Drug Administration (FDA) approved the first drug for this condition. It has been shown to decrease symptom severity and disease progression but requires regular intrathecal or spinal injections. In May of 2019 the FDA approved the first gene therapy for SMA patients. The therapy only requires one intravenous injection that has been shown to improve muscle movement and function as well as survival rates. Long term studies are still underway and there is a substantial financial cost associated with the therapy. Currently, structuring of the SMA NBS follow up process are under development.

New Condition Challenges

While early detection and treatment has been shown to improve outcomes for most individuals with the above conditions, adding these conditions to the Florida NBS has had its challenges. A lack of genotype-phenotype correlation for X-ALD means that late onset individuals will receive early medical management unnecessarily and currently, no published study has directly compared treatment outcomes for those detected pre-symptomatically and those diagnosed after the development of signs and symptoms (Bodamer, Scott, & Giugliani, 2017). Pompe and MPS1 have also posed new challenges to laboratories conducting NBS because of what is called pseudodeficiency. This refers to a change in the gene sequence that reduces the gene product but not enough to cause the disease. In these instances, the baby would most likely be flagged on the NBS and the sample would undergo two more levels of testing to determine whether the infant truly has the condition. Because timing of medical intervention is especially import in severe cases of Pompe disease, labs will be reporting results after Trier 2 testing, while the sample continues to Trier 3 confirmatory genetic testing. This may increase false positive reporting but will ensure that the most severe cases receive necessary treatment. In the case of SMA, treatment costs range in the millions of dollars, raising the issue of access and affordability.

Conclusion

The NBS plays a crucial role in the early detection of rare genetic disorders for newborns, providing caregivers the opportunity to mitigate the long-term effects of these rare genetic disorders. Although challenges in diagnosis, treatment, funding, and educating the medical community add to the complexity of these conditions, they give the opportunity to improve the lives of patients with these disorders. Given the importance of the screen to patients and their families, it is imperative that we stay informed of the latest developments in disorder inclusion and the treatment options available to those affected.

Resources

ACMG Newborn Screening Act Sheets, htttp://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm

American Academy of Pediatrics, https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Newborn-Screening.aspx

Florida Department of Health, http://www.doh.state.fl.us

Baby's First test, https://www.babysfirsttest.org/

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About the RCPU
The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.
Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

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