Screening for Severe Combined Immunodeficiency Disease

By Amy Scanlin, MS

Screening for SCID saves thousands of newborns' lives each year, costs far less than screening later and has resulted in the identification of new types of this deadly disease.

Severe combined immunodeficiency disease (SCID) is a pediatric emergency caused by genetic defects that create havoc on the immune system. Babies born with SCID (about one in every 30,000 to 50,000) have little to no T cell function to defend them against infections, and if not treated during their first months of life, they will die. Those who do receive treatment have a 94 percent chance of survival.

Thankfully, about 55 percent of infants born in the U.S. are now screened for SCID (more than two million so far nationwide) and other conditions that cause low T cell counts. Screening is conducted using T cell receptor excision circles (TRECs) screening. The TREC assay allows for diagnosis of newborns before symptoms have developed, which results in lifesaving treatment.

TREC screening "is so important because this is the only way to determine if a child has SCID," says Fred Modell who founded the Jeffrey Modell Foundation (JMF) with his wife Vicki in memory of their son who at age 15 died of an infection brought about by a primary immunodeficiency disease (PI). "These newborns look great; they have rosy cheeks and bright eyes, and without this testing, they will begin very early on to develop overwhelming infections, and they won't survive. But, when we can screen for and identify SCID, we can do a bone marrow transplant very early on, and these kids don't just improve, they are cured!"

What Is TREC Screening?

TRECs are DNA molecules formed within maturing T cells that develop in the thymus and are measured by a technique called polymerase chain reaction (PCR). Normal blood samples have one TREC per 10 T cells (a good result indicating a high rate of T cell development), while babies with SCID and other related conditions either have very low T cell numbers or lack T cells altogether.[1]

TREC testing is conducted via dried blood that is collected onto filter paper from a heel stick. From this dried blood spot (DBS), a very small sample is punched out and tested. Testing is so efficient, that public health laboratories can actually test thousands of DBSs at one time.

If the result of the TREC assay indicates low levels of T cells or PCR failure, blood samples are drawn and a process called flow cytometry is performed to look at the total lymphocyte numbers and subsets of T, B and natural killer cells, as well as naïve and memory T cells.[1] Infants may also go through genetic testing.

Because early testing is conducted on such a large scale, the vast majority of tests will have a negative result. Babies who test positive, however, now have a very good chance of survival. It should be noted that premature babies have the highest incidence of false positives.

What Does the TREC Assay Identify?

"The TREC newborn screening has revealed a wide spectrum of non-SCID disorders and led to better understanding and treatment of these conditions," says Emily Hovermale, senior public policy manager for the Immune Deficiency Foundation (IDF). "It has led to the discovery of new types of SCID that were not previously known, now being classified as variant SCID."

The most widely recognized condition identified by TREC screening, and the most deadly, is SCID. There are several forms of SCID with the most common linked to the X chromosome that mostly affects males as they only have one X chromosome, while females have two and are more commonly carriers. A TREC screen will also identify conditions such as Omenn syndrome (also known as leaky SCID), DOCK8 deficient hyper-IgE syndrome (also a severe PI), Trisomy 21 (Down syndrome), DiGeorge syndrome, CHARGE syndrome, Jacobsen syndrome and cartilage-hair hypoplasia, as well as low T cell counts brought on by other conditions such as neonatal cardiac surgery and leukemia.

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SCID is a PI that at first appears to be persistent infections that don't resolve with normal treatments. Symptoms including severe respiratory infections, rashes that look like eczema, persistent diarrhea, thrush and pneumocystis pneumonia, which is the real red flag infection that should be an indicator a baby should be tested for SCID. Babies with SCID have severely impaired immune systems that cannot fight off infections and may have multiple hospitalizations before they are diagnosed, assuming they are not identified early through the TREC assay.

Omenn syndrome (leaky SCID) is caused by a mutation in the RAG1 or RAG2 genes and is characterized by peeling and red skin, diarrhea, enlarged lymph nodes, as well as elevated IgE levels and T cells (though the T cells are not functioning properly). Low IgA, IgG and IgM levels and virtually no B cells are also indicators. Babies with Omenn syndrome develop similar infections to other types of SCID and have the same prognosis if not identified and treated early.

Dock8 deficient hyper-IgE syndrome (HIES) is a rare PI characterized by skin conditions such as eczema and abscesses, as well as high levels of IgE. Mutations and

deletions in the DOCK8 gene are found to be the cause of most of the autosomal recessive (type 2) type, while the genes encoding the transcription factor STAT3 (not identified by the TREC assay) cause most of the more common autosomal dominant (type 1) type. Dock8 HIES is an inherited trait in which 95 percent of those affected have an error in chromosome number 9.

Trisomy 21 (Down syndrome) is a genetic condition in which one has 47 chromosomes instead of 46. In most cases, chromosome 21 is the error. It is one of the most common birth defects and may include additional conditions such as cataracts, dementia, hearing problems, breathing problems causing sleep apnea, as well as an underactive thyroid.

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DiGeorge syndrome (22q11.2 deletion syndrome) is one of the most common conditions identified, and is a syndrome with more than just SCID, according to Michael S. Watson, PhD, FACMG, executive director of the American College of Medical Genetics and Genomics. It may first become evident through a variety of types and severity of issues such as a heart defect, cleft palate and impaired immune function, as well as behavioral problems. Babies appear weak with poor muscle tone and have trouble gaining weight due to difficulty feeding and frequent infections.

CHARGE (coloboma, heart defect, choanal atresia, retarded growth and development, genital abnormality and ear abnormality) syndrome often results in multiple life-threatening conditions such as a hole in an area of the eye called the coloboma, narrowed (choanal stenosis) or completely blocked (choanal atresia) nasal passages, and cranial nerve damage that diminishes sense of smell. It can cause facial paralysis and hearing loss.

Jacobsen syndrome (11q terminal deletion disorder) is caused by loss of genetic material from chromosome 11. While symptoms vary considerably, most have delayed developmental growth and possible learning disabilities. As children develop, they may have heart defects, a blood platelet disorder called Paris-Trousseau syndrome that causes abnormal bleeding and easy bruising, difficulty feeding and skeletal issues. Jacobsen syndrome in most cases is not inheritable, but it is caused by random deletions during early reproductive cell development. Those who have the deletion may pass it on to their children.

Cartilage-hair hypoplasia is an autosomal recessive genetically inherited bone growth disorder resulting in dwarfism, impaired immune function and infections due to bacteria and viruses.

There are some conditions TREC testing will not diagnose because the circulating T cell levels are above the cutoff. Examples are major histocompatibility complex (MHC) class II deficiency, a rare autosomal recessive form of combined immunodeficiency with similar symptoms to SCID,[2] and a rare autosomal recessive form of SCID. Alternative testing strategies need to be developed to identify those with these type of immune deficiencies.

TREC Screening Economics

TREC screening has a high rate of accuracy, which results in significant cost savings. According to Dr. Watson, the TREC assay's "clinical accuracy varies a bit since there are many forms of SCID. Screening for the most severe forms of T cell lymphopenia is very accurate, while some of those with partial or variant forms of the disease can be harder since they may have partial function of the process."

However, Dr. Mei Baker, co-director of the Newborn Screening Laboratory at the Wisconsin State Laboratory of Hygiene, reports that the state of Wisconsin has a 99.98 percent specificity in about 400,000 screenings since the adoption of TREC screening in 2008. This is not only a great percentage but a great percentage at a very low cost. For example, when adopted in Wisconsin, the TREC test cost about $6.50, in part because the state already had infrastructure in place. The cost of the screenings overall depend largely on a state's birth rate. States with lower birth rates will have lower costs because they need fewer machines, smaller labs and fewer staff. Modell suggests costs can even be as low as $4.25 per test. However, adds Dr. Baker, any cost of newborn screening is far less than the costs of ruling out a condition later, both financially and emotionally. "This is a positive predictive screening," she says.

According to Hovermale, in approximately one million babies in two years screened in California (the largest number of screened cases in any state), one in 19,900 babies had a significant T cell lymphopenia. For all forms of SCID (typical SCID, leaky SCID and variant SCID), there was a combined incidence of one in 49,700. This compares

with earlier estimates of SCID incidence at one in 100,000 and no real known estimate of the incidence of all T cell lymphopenias.

"We ran a full economic analysis and decision tree," adds Modell, "of what the costs of testing are versus not testing. When we don't screen, and just treat as we go, it costs about $2 million to let the baby go through intensive care treatments and try to keep them alive. If they don't receive a bone marrow transplant within six months, their bodies may reject the transplant due to overwhelming infections. But if we screen and identify early, we can manage it, treat it, and the baby will live a normal life. That treatment will cost about 25 percent of the costs of a SCID baby not screened."

Hovermale also provides an economic analysis for the state of Washington: "Recently, Washington state developed a cost-benefit study in conjuncture with their argument to add SCID, which found the benefit–cost ratio of screening for SCID was 4.36, meaning that for every dollar of costs to provide SCID screening, there will be $4.36 worth of benefits."

Grass-Roots Campaigns

In 2010, then-Health and Human Services Secretary Kathleen Sebelius added SCID to the list of 29 disorders recommended for population-based universal newborn screening. This addition was the first to be recommended by the Advisory Committee on Heritable Disorders in Newborns and Children since its founding in 2003. However, because this is a recommendation, it is up to each state to decide whether to add TREC screening for SCID to their newborn screening program.

Wisconsin was the first state to add TREC screening for SCID in 2008, followed by Massachusetts, California and New York. Many other states have also added TREC screening, including Colorado, Connecticut, Delaware, Florida, Iowa, Michigan, Minnesota, Mississippi, Ohio, Pennsylvania, Texas, Utah, Washington, Wyoming and the territories of the Navajo Nation. States that are set to add the testing to their panel include Missouri, Nebraska, North Dakota, Rhode Island, South Dakota and West Virginia. Still others have approved the testing but have a longer timetable for implementation. These include the

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District of Columbia, Georgia, Illinois, Maryland, Maine, North Carolina, New Jersey, Oklahoma and Virginia. JMF was instrumental in getting state-level screening off the ground by committing funds to help states get started.

According to Dr. Baker, all states are interested in adding SCID to their newborn screening programs. "Implementing it is the right thing to do," she says. Why some states have already adopted and others have not depends largely on time and funding. "They've got to get the budget and figure out where the money is coming from," she explains. "It's a new area for many, and we have a lot of states in different stages of adoption. We plan to see a lot of new states adding the screening in 2014 and 2015."

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"There may also be issues of available equipment and space," explains Dr. Watson. "The TRECs assay is among the first molecular tests for many of the labs, so training to use it may be needed. This isn't as big an impediment for TREC since it isn't a gene but is, rather, a product of a normal process that results in small pieces of DNA that get clipped out of sequences that create immune responses to different types of exposures. Some labs may even have space issues for adding more tests to their menus."

Unfortunately, at present, the Affordable Care Act (ACA) does not offer much assistance to parents with regard to covering testing. "The ACA is quite thin with regard to genetics. While it does include prevention, which is what newborn screening is all about, there is little specificity as to what it applies to," says Dr. Watson. What the ACA does cover are essential health benefits. These "mostly address the diagnosis and treatment of the condition rather than the screening, which is a state function that is paid for by state funds, Title 5 funds from the feds, or through fees that are passed on to those being screened," adds Dr. Watson. "We are working to have the diagnosis and treatment of conditions identified in newborn screening added to the essential health benefits since, without them, some kids could fall through the cracks of coverage."

Grass-roots efforts are underway to not only keep the pressure on states to add SCID screening but also to provide educational and advocacy materials to families. "The newborn screening system is not just a lab test," says Dr. Baker. "Education plays a huge role from primary care physicians to family members." IDF says now that screening is on the table, the real work of education across the board can begin. "Since the addition of SCID to the Recommended Uniform Screening Panel, we have had about 50 grass-roots volunteers working in 30 states to get SCID added to their state newborn screening panel," says Hovermale. "One of the most impactful things that these advocates do is to participate in the newborn screening advisory committee meetings that states have to recommend which conditions get added to the state newborn screening panels. When these advocates, who are usually parents of patients (some of whom have passed away), give their testimony and share their stories, they put a face on this disease. It is hard to tell a parent who has lost a child that this test is not worth doing."

"The newborn screening program as a whole is one of the best examples of a public health program," adds Jan Klawitter, public affairs manager at the Wisconsin State Laboratory of Hygiene. "From labs to follow-ups, to genetic counselors to nutritionists, this is prevention at its most basic. Patients who are identified can start on a treatment, and they can hopefully have a much better outcome."

"This is just a great story that was thought to be impossible only a few years ago!" adds Modell. ■

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