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Lessons for Sequencing from the Addition of Severe Combined Immunodeficiency to Newborn Screening Panels

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In 2008, the DHHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was asked to consider adding disorders to the recommended uniform panel of newborn screened diseases. The first disorder nominated was severe combined immunodeficiency (SCID), a collection of rare defects in genes controlling development of the adaptive immune system.[1] SCID was judged to meet the Committee's criteria for inclusion in newborn screening, being a disorder that profoundly affects the health of infants, while also being treatable and, with the development of a new test, amenable to detection. Now widely adopted, SCID newborn screening (NBS) has proven effective for early identification and treatment of SCID. In addition, screening has improved our understanding of SCID and related disorders, which are more diverse than originally believed.[2] NBS for SCID illustrates how adding new disorders to newborn screening panels can be enormously beneficial if evidence-based guidelines are adhered to and if mechanisms are in place to track outcomes and learn along the way. These lessons should guide all additions to newborn screening, including those involving sequencing.

SCID was not only the first condition nominated to the Secretary's Advisory Committee, but also the first immune disorder considered and the first with a screening test performed on DNA.[3] SCID NBS has thus brought DNA technology into screening laboratories and opened the door to its wider use for additional conditions.

Infants born with SCID typically appear normal at birth, but have severe impairment in production of T lymphocytes combined with absent or defective B lymphocytes that fail to produce protective antibodies. Lacking T and B cell function, infants with SCID are at high risk for life-threatening infections, particularly after two months of age when maternally transferred immunoglobulin has waned. Treatments for SCID replace the faulty immune system, usually by means of transplanting blood-forming stem cells of the bone marrow from a healthy donor. An HLA-matched sibling is the ideal donor, but infants may also receive life-saving transplants from haploidentical parents or matched unrelated donors.[4–6] In addition, enzyme replacement injections can restore immune cell viability for infants with SCID due to adenosine deaminase (ADA) deficiency, and experimental gene therapy is available and appears highly successful for X-linked SCID and ADA-SCID. The best survival and health outcomes for SCID are achieved if immune restoration is performed early in infancy, before onset of infectious complications.[7–8]

In the past only SCID-affected infants with a recognized family history – fewer than 20% of cases – were diagnosed early.[8] Timely diagnosis and treatment for all infants, not just those

with a positive family history, requires population-based screening. In 2009, after reviewing the initial evidence, the Advisory Committee ruled that SCID could be eligible for inclusion in the recommended panel if the proposed screening test proved, sensitive, specific and cost-effective. This test, based on amplification of circular DNA byproducts called TRECs, was then piloted in Wisconsin, Massachusetts and the Navajo Nation, becoming the first primary screening test to use DNA isolated from standard dried blood spots.[9–12] In 2010, the Secretary's Advisory Committee voted unanimously to recommend universal SCID NBS.

The TREC test detects over a dozen genetic causes of SCID as well as what is known as "leaky SCID" where more but still insufficient T cells are produced.[2,13] Prior to NBS, the heterogeneous phenotypes of leaky mutations meant that some affected individuals were not diagnosed until later in childhood. The TREC test also detects other conditions in which there is abnormal loss of T cells from the peripheral circulation. These "secondary targets" of the TREC test include certain genetic syndromes in which T cells can be affected, such as DiGeorge syndrome, as well as non-immune disorders such as congenital leukemia, vascular leakage, and prenatal exposure to immunosuppressive medication.

Whatever the cause, infants with very low T cell counts have impaired immunity and are referred to pediatric immunologists. Interventions may include avoidance of live vaccines, protection from infectious exposures, administration of prophylactic antibiotics and immunoglobulin infusions, and in some, hematopoietic cell transplants.[2,14]

In addition to identifying infants in need of treatment, NBS for SCID has improved understanding of the disease. In particular, screening has revealed that the distribution of genes causing SCID includes a smaller proportion of X-chromosome linked genes than was previously reported, possibly reflecting greater ascertainment of cases with autosomal recessive mutations and no family history. Additionally, genes not previously known to be associated with SCID have been discovered. Indeed, compared to cases reported in the pre-screening era, a higher proportion of NBS SCID cases lack known gene defects, even after panels of typical SCID genes are sequenced.[2,13]

In the U.S., all newborns screening laboratories that perform TREC testing have followed the general guidelines issued by the Clinical Laboratory Standards Institute.[15] However, different programs have developed their own TREC cutoffs and rules for handling testing of ill and preterm infants. Thus, not all programs have the same criteria for recalling infants for additional specimens, referral to specialists for follow-up, and immunological investigations undertaken after non-normal TREC results. A recent study compared SCID NBS outcomes in over 3 million infants screened by 11 programs in the U. S.,[2] reporting that 1 in 58,000 infants have SCID or leaky SCID, nearly twice the incidence estimated prior to screening. The authors noted that, despite some variability in testing practices, all programs readily detected infants with typical and leaky SCID, no SCID cases were missed by NBS and then detected later, and affected infants underwent immune restorative treatments in a timely fashion.

The central idea of screening leading to early disease detection and treatment is simple. However, the path to its successful implementation (on the one hand, bringing to treatment

those with previously undetected disease, and, on the other, avoiding harm to those not in need of treatment) can be complex. Differences between state TREC NBS programs provide alternate models that are potentially instructive, if systematically compared.

Today, newborns are screened for SCID in 47 U. S. states, Puerto Rico, and the District of Columbia, with Israel, New Zealand and Norway performing nationwide screening and other countries advancing plans and pilot programs. This population-based screening has enabled a more accurate determination of the incidence of SCID and changed our understanding of its clinical presentation from one dominated by infections and failure to thrive to healthy-appearing infants who are nonetheless very small, very young and very immune compromised. Large multi-center collaborations, such as the Primary Immune Deficiency Treatment Consortium, have been established to define and investigate the impact of many variables involved in treating these infants.[5,6,13] Many choices are now tailored to specific genotype, including whether to use gene therapy and selection of a chemotherapy conditioning regimen.

The SCID screening assay quantitates the TREC biomarker for T cells that happens to be composed of DNA. Thus, while babies' DNA must be isolated for the TREC assay, no sequencing of specific disease-associated genes or of a patient's exome or genome is involved. Although the targeted use of DNA for TREC testing does not raise the same ethical challenges that WES or WGS would, it opens the door to wider applications (i) by showing that it is straightforward to obtain from dried blood spots sufficient DNA for other purposes; and (ii) by energizing advocates for non-SCID conditions without a readily ascertained biomarker, but for which deep sequencing might allow early detection and earlier treatment. DNA is routinely isolated and used in NBS laboratories today. The future challenge is to establish how it should be used for sequencing, and the SCID experience suggests that benefit can accrue, provided evidence-based guidelines are developed and strictly followed.

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