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A Brief Note on T-Cell Receptor Excision Circles

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Editorial Note

The California NBS program's interpretation of TREC data; each programme has established its own interpretation algorithms and cutoffs, but the fundamental approaches are comparable. The control gene is not included in the first TREC qPCR run in California and many other programmes, primarily to save money. If the initial TREC value is less than the programme cutoff, the analysis is redone using the same DBS specimen, but this time with the control gene included. If the control gene does not amplify in this second analysis, a new DBS material is required.

If the control gene amplifies but the TREC value remains low, the infant will be referred for additional testing, which is done as a follow-up test in California. For DBS with undetectable or very low TREC values but sufficient control DNA amplification, most NBS algorithms offer a "Urgent positive" limit. Infants with Urgent positive readings are at a very high risk of SCID, so their care is prioritised. Infants who appear healthy but have Urgent positive TREC results are promptly referred for flow cytometry lymphocyte subset identification and evaluation by a paediatric immunology specialist. Infants who appear to be healthy yet have a positive but non-urgent TREC result are also referred.

For various reasons, low birthweight, preterm, and ill infants cared for in a Neonatal Intensive Care Unit (NICU) have a higher rate of false positives or unacceptable results for all NBS tests; in a recent California report, NICUs accounted for only 9% of births, but were the source of 47% of TREC test results that were positive or had poor control DNA amplification, even after obtaining a repeat DBS.

Many NBS programmes have a policy of collecting a second NBS samples from NICU infants every two weeks. At 28 days, some people take a third sample. Waiting until the second specimen is collected permits the infant's immune system to mature, potentially resulting in normalised TREC levels. Low TREC readings in this group may simply reflect prematurity because extremely preterm and low-birth-weight newborns have fewer lymphocytes than term infants.

A total blood cell count, differential count, and lymphocyte subsets by flow cytometry, including naive and memory phenotypic helper and cytotoxic T cells, as well as B and natural killer cells, are the follow-up tests for infants who do not have normal TREC results. Infants who are no longer hospitalised must be recalled to a phlebotomy centre for this level of testing since a liquid blood sample is required. Although flow cytometry can diagnose SCID quickly, other tests of T-cell activity, lymphocyte proliferation assays, and maternal engraftment of T cells, as well as gene sequencing, are usually necessary to establish a specific form of SCID.

Flow cytometry testing should, in an ideal world, be coordinated by the NBS programme, as it is in California. When compared to screening programmes that stop being involved after reporting abnormal TREC results, we've discovered that there are various advantages to this. Most importantly, because NBS should be considered as a programme rather than a test for identifying newborns with serious, treatable disease, it is in the public interest to ensure that all infants with SCID receive prompt treatment from appropriate professionals.

If programmes do not include a standard level of flow cytometry testing, some infants, particularly those from low-income families or those who live in rural areas, may face insurance authorization delays or receive testing that is not as informative as it should be, requiring more iterations and time to reach a diagnosis. It's also critical for NBS programmes to collaborate closely with a network of paediatric immunologists who specialise in neonates and are aware of the need of keeping health-care expenses under control.

Some doctors may feel compelled to request tens of thousands of dollars' worth of tests on a first visit, the majority of which will be unnecessary because at least half of all infants with positive TREC test findings will have normal flow cytometry results. Not only does uniformity of testing and interpretation of results ensure that infants with abnormal TREC screens receive quick, high-quality care, but it also allows the programme to track results and outcomes and make adjustments as needed for quality improvement.