

Correspondence

Reply

To the Editor:

Collier et al¹ suggest an alternative method to screen newborn populations for severe combined immunodeficiency (SCID). They point out that collection of cord blood for flow cytometric analysis, which incidentally identified a case of SCID in their hands, could be an alternative to the assay of T-cell receptor excision circles (TRECs) in DNA isolated from dried blood spots, as described in my article.² They allude to the Barwon Infant Study, in which (according to the study Web site) a total of 1000 cord blood samples are planned to be collected eventually at 2 hospitals over 5 years.^{3,4} They gloss over the challenges of scaling up the Barwon protocol, including transporting liquid blood from all deliveries in a population-based screening program to centers that would perform flow cytometry. Moreover, neither their correspondence nor the reference they cite contains any data on the number of infants enrolled to date; the number of samples analyzed; the proportion of infants born whose samples were not collected, were unsatisfactory, or both; or other information required to compare the flow cytometric method with TREC analysis.³ Such data would be essential to formulate a meaningful comparison, and tens of thousands of term and preterm births across the entire range of birthing centers would need to be screened to establish whether cord blood flow cytometry is in fact amenable to large-scale universal testing. The limited markers mentioned, CD3, CD4, and CD45, would not take the place of a more detailed lymphocyte subset analysis for definitive diagnosis and could lead to false-negative results (ie, missing true cases of SCID) if maternal blood or lymphocytes were present in the samples. Because flow cytometry is not currently used by any newborn screening laboratories, there might be no advantage to addition of this platform versus addition of DNA-based testing, which promises to be useful not only for TREC measurement but also for tests in the future for a wide array of disorders.

Now that more than one million newborns in California alone have been screened with the TREC assay for SCID and other clinically significant T lymphocytopenic disorders, it is clear that this method has an extraordinarily low rate of false-positive results on the initial sample (<0.1%). Furthermore, despite the statement by Collier et al¹ regarding TREC dried blood spot tests

that “less than 10% of infants with low TREC counts are subsequently shown to have SCID on further testing,” in California 40% of infants referred to flow cytometry have had clinically significant T lymphocytopenia (<1500 CD3 T cells/ μ L), requiring intervention to avoid live rotavirus vaccination and other complications, even if typical SCID was not confirmed.

Finally, readers might be skeptical that a cost of \$4 per sample would cover collection, processing, analysis, and data management of large numbers of liquid cord blood samples in their own localities.

Nonetheless, newborn screening for immunodeficiency is in its infancy, and it might not be the case that the TREC test is the only one that will succeed in every setting. Ideas for assays that could be used for the diagnosis of a wider range of diseases, such as combining TREC and B-cell excision circle testing,^{5,6} or that offer greater clinical efficacy at lower cost deserve consideration.

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