Bias in *CFTR* screening panels

To the Editor: The comparison of *CFTR* mutation screening panels with population frequencies using data from the Exome Aggregation Consortium carried out by Lim and colleagues[1] highlights the continued gap in annotation of variation in *CFTR*. The Exome Aggregation Consortium cohort presents a much more ethnically and geographically comprehensive sampling of individuals than the collections of cystic fibrosis (CF) patients from which mutation screening panels are derived. The authors therefore conclude that the sensitivity of CF screening could be improved by replacing panels with exome sequencing.

Sequencing has an important role in CF patients with defined phenotypes and will enhance understanding of the role of *CFTR* variants in non-European individuals who present with phenotypic features not readily recognized as CF.

However, we feel that sequencing is not a better way to achieve the goals of carrier screening. Carrier screening has traditionally focused on variants that have known, life-threatening consequences in order to enable unaffected heterozygous patients to make informed reproductive decisions.[2] Sequencing and the potential identification in screened individuals of uncharacterized variants that may have reduced penetrance promotes selection against relatively benign phenotypes along with true disease-causing conditions. Furthermore, the use of computational mutation prediction scores from PolyPhen-2 and PROVEAN are too imprecise and undervalidated for clinical decision making because they lack specificity.[3] For example, a variant with a slight effect on reproductive fitness (such as those associated with only obstructive azoospermia) is categorized as pathogenic in the same fashion as a variant that is fully penetrant for life-shortening CF. Therefore, the authors may be overestimating the number of CF-causing mutations that go undetected on traditional carrier screens. Indeed, the lack of information to adequately counsel an asymptomatic carrier with an uncharacterized variant is an important unmet challenge in implementing personalized medicine.[4]

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DISCLOSURE

The authors declare no conflict of interest.

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Response to Sosnay *et al*.

To the Editor: We thank Drs Sosnay et al.[1] for their thoughtful comments. Their commitment to *CFTR* research continues to add valuable clarity to the clinical and functional consequences of *CFTR* genetic variation.

We set out to quantitate what we as a genetics community have been aware of for decades: cystic fibrosis carrier screening does not adequately identify reproductive risk among non-European populations. Current "pan-ethnic" carrier screens stipulate as much,[2] and yet *CFTR* is among the most rigorously studied and well-covered disease genes.

New pathogenic variants are currently added to ClinVar on a monthly basis, and affected children continue to be diagnosed with novel variant combinations. Thus, clinically-based pathogenic data sets will always be incomplete. We believe it is our obligation as genetic researchers to acknowledge this complex reality while utilizing the full force of scientific progress to illuminate disease risk in all populations. One crucial step in this direction is the adoption of exome sequencing as the standard for reproductive risk analysis. Exome sequencing provides an opportunity to level the analytic playing field. It eschews the restrictions and population bias inherent in targeted mutation testing. Further, exome sequencing sets the foundation for a sophisticated interpretation of genetic variation and reproductive disease risk.