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]

ACKNOWLEDGMENTS

The CFTR2 project is funded by unrestricted educational grants from the US CF Foundation, Vertex Pharmaceuticals, and Sequenom, Inc.

DISCLOSURE

The authors declare no conflict of interest.

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Advance online publication 29 October 2015. doi:10.1038/gim.2015.105

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.

PolyPhen-2 and PROVEAN are examples of tools that are starting to answer the call for variant interpretation in the absence of clinical data. We champion these efforts to create and improve on existing methods and data sets, which may eventually be used to find clarity in disease potential at stages before diagnosis. We have also developed a publicly accessible resource to assist in this effort.[3]

In our analysis of *CFTR* carrier screening, these tools demonstrate important gaps in current approaches to *CFTR*-related risk. By using them to identify likely disease-contributing variants hidden from current carrier screens, our goal was not to surface variants that should be added to screening panels; instead, we set out to highlight an inherent limitation in the carrier screening framework. These tools, and the innovation they represent, are highly relevant to the development of a more effective response to disease risk identification and management for all patients.

We believe that a combination of tools, incorporated into a dynamic and complex analytic methodology, will be most valuable for determining reproductive risk in novel scenarios. This need has been identified elsewhere, most recently described by Evans et al.[4] as an "infrastructure for continuous learning." As we move together toward a more complete understanding of the human genome, we will achieve better detection of disease risk. However, fulfilling this critical goal also requires new analytic and clinical approaches. We are pursuing improved detection with an alternative methodology that will challenge the way we think about reproductive disease risk.

DISCLOSURE

R.M.L., A.J.S., M.J.S., C.B., B.S., J.L.L., and T.C.P. are currently employees at GenePeeks, Inc. L.M.S. is currently a consultant for GenePeeks, Inc.

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Advance online publication 29 October 2015. doi:10.1038/gim.2015.106