

term needs to be considered and measured, as well as what carrier individuals and couples actually do with the information. Thus, carrier panels lower the cost of testing but could conversely increase the other costs of a carrier screening program.

Furthermore, the vast majority of conditions included in the panel are extremely rare; at least 30 conditions have an incidence of <1 in 1 million, and all but a handful occur in <1 in 5,000 individuals (ironically, α -thalassemia, perhaps the most common genetic disease in the world, is not included in the panel, we presume for technical reasons). Therefore the likelihood of follow-up carrier testing identifying a mutation in the partner is expected to be small.

In this study, 127 carrier couples (0.54% of all patients who underwent testing) were identified. Of note, 47 of these cases were positive for α -1-antitrypsin deficiency, with both the S and Z allele included in the panel. The S allele is known to be common in some populations and is not thought to be of much clinical importance unless paired with a more severe allele, and even then would be expected to cause a milder phenotype. On removing α -1-antitrypsin and the conditions for which screening guidelines already exist (through the American College of Obstetricians and Gynecologists and/or the American College of Medical Genetics and Genomics), such as cystic fibrosis, sickle cell anemia, β -thalassemia, spinal muscular atrophy, Tay-Sachs disease, the detection of carrier couples would drop to <0.1%. Included in this figure are conditions such as familial Mediterranean fever, factor XI deficiency, and *GJB2*-related hearing loss. Considering the mild and variable phenotype, age of onset, and treatment options for conditions such as these, significant ethical dilemmas accompany including these on a preconception/prenatal carrier screening panel.

Apart from the cost argument for increased screening, the authors suggest that the increasing population ethnic admixture is further justification for expanded “panethnic” carrier testing. Although we agree that the increasingly diverse background of the US population presents new carrier screening and risk assessment challenges, the possibility that this increased diversity may actually be decreasing the incidence of recessive genetic disease should be considered. The authors state that the “data show a number of severe Mendelian disorders are more prevalent than commonly understood.” On the basis of the presented data, there was nothing to show an increased incidence of disease. The carrier frequencies were higher than previously reported for some conditions and lower than previously reported for others, but there is no measure of prevalence of these recessive conditions.

The stated carrier frequencies do not take into account the possibility of ascertainment bias in what is not likely to be a random sample of the population. For example, a couple from a population with a low incidence of a particular recessive disorder might happen to have a family history of the disorder, which led them to undergo the testing in the first place. This would elevate the apparent carrier frequency in the population. The possibility of ascertainment bias is suggested by the identification of 78 homozygotes/compound heterozygotes. This

could mean that at least some people are undergoing carrier testing as a means of diagnosing a genetic disease.

We hope we can reflect on the long held important considerations for implementing population screening programs and carefully weigh the pros and cons of expanding screening for our patients and for society.

DISCLOSURE

K.S. and R.R. declare no conflict of interest. K.S. is an employee of the Department of Defense, but the views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US government.

Katie Stoll, MS¹ and Robert Resta, MS²

¹Department of Obstetrics and Gynecology, Madigan Healthcare System, Tacoma, Washington, USA; ²Swedish Medical Center, True Family Women’s Cancer Center, Seattle, Washington, USA. Correspondence: Katie Stoll (katie.stoll@us.army.mil)

REFERENCE

1. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med* 2012; e-pub ahead of print 13 September 2012.

doi:10.1038/gim.2013.18

Open

Response to Stoll and Resta

To the Editor: We thank Stoll and Resta¹ for their feedback on our data in their letter titled “Considering the Cost of Expanded Carrier Screening Panels,” and welcome discussion on the merits of expanded carrier screening. We understand this is the beginning, not the end, of genomic applications in reproductive care and fully expect that enhancements will continually increase the test’s efficacy. As we consider the correct path to a test’s maximal clinical utility, an analogy to prenatal screening for Down syndrome seems applicable.

Down syndrome screening began with crude risk estimates based on maternal age. Introduction of the α -fetoprotein biochemical assay improved sensitivity, but it was still poorly reliable by current standards. False reassurances occurred, as did difficulties regarding counseling and results interpretations. Nonetheless, these tests were implemented. They represented an improvement over contemporary approaches but did not signal the end of related research. Today, the options for prenatal aneuploidy screening are more promising than ever and yet still merit further refinement. Similarly, expanded carrier screening represents a vast improvement over an ethnicity-based approach for a small number of diseases, and routine implementation can serve to further development.

We are first obliged to address specifics from the correspondents' letter. They make a factually incorrect assertion: in the disease list of the original study, the detection rate is actually 80% or greater in at least one ethnicity for more than half ($n = 55$) of the diseases and is more than 50% for almost all ($n = 84$). Panethnic screening by targeted genotyping results in a given ethnicity experiencing a lower detection rate for a subset of diseases. We believe this approach is acceptable for the ease of having a single protocol, in contrast with the ethnic stratification approach, because of the substantial limitations we described in the original paper and that were acknowledged by Stoll and Resta.

The authors call for more investigation into clinical outcomes, counseling resources, and ultimately, clinical guidelines issued by the relevant professional organizations. We eagerly await these guidelines and will continue to furnish data to support the field's development. Reasonably, organizations such as the American College of Medical Genetics and Genomics aim to make evidence-based recommendations. Therefore, data creation through testing implementation is a necessary first step. Individual use of the test prompts guidelines, not vice versa. Noninvasive aneuploidy testing of cell-free fetal DNA is a most recent example of this ordering.

Stoll and Resta express concern about costs associated with follow-up testing, including gene sequencing, and posit that these should be included in the total cost of a carrier screening program. Using cystic fibrosis as an established standard, panethnic carrier screening was implemented despite reduced ethnic-specific detection rates and expensive sequencing.

They also suggest that the diseases tested are too rare by noting that most have a prevalence of <1 in 5,000 individuals. Mendelian diseases, by their very nature, are uncommon. A 1 in 5,000 prevalence strikes us as an unreasonable threshold because few monogenic diseases exceed it. In fact, many diseases already endorsed for screening by the American College of Medical Genetics and Genomics occur with a lower frequency, including spinal muscular atrophy.

"Rare" must be examined in light of the ability to analyze genes in a multiplex fashion. In fact, ~ 1 in 400 US births is affected by a disease in our original study. According to the criteria for general population screening established by the World Health Organization in 1968, "a disease need not have a high degree of prevalence to be considered an important problem."² Individually rare diseases, when viewed collectively, are acknowledged to occur with common frequency and confer significant public health and patient burden.³

Finally, psychosocial implications of carrier screening have been exhaustively studied. A recent meta-analysis of long- and short-term effects concluded that (i) anxiety was overridden by knowledge of reproductive options and may

be allayed by counseling services, and (ii) guilt was significantly associated with individuals who discovered carrier status after they had an affected child (i.e., "survivor guilt").⁴ On the basis of this, one may conclude that the benefits of testing more often outweigh the risks, and that the effects of not testing carry potentially greater psychosocial risks. Many similar conclusions have been drawn on persons who have undergone genomic analysis.

As genomic technologies continue to advance, we look forward to their many positive contributions to the health of our populations while pursuing the answers to ensuing difficulties. While this undoubtedly long process unfolds, we consider the bioethical principles that guide medical care. The suggestion of an "ethical dilemma" by the authors may strike a dissuasive chord. Yet a fundamental ethical principle Stoll and Resta do not address is respect for a patient's autonomy. Current carrier screening models hinge critically on personal, not provider, values regarding reproductive autonomy. Given that screening remains voluntary, we argue for allowing individuals the self-determination of their reproductive options, with the benefits and limitations that accompany them. Patients, by and large, are able to weigh and decide on complex information, as they do every day in all parts of medicine. A more significant ethical problem, then, is to not provide patients the opportunity to learn and act on information that can be easily gained with today's technological resources.

DISCLOSURE

All authors are employees of Counsyl.

Gabriel A. Lazarin, MS¹, Imran S. Haque, PhD¹, Shivani Nazareth, MS¹ and Eric A. Evans, PhD¹

¹Counsyl, South San Francisco, California, USA. Correspondence: Eric A. Evans (eric@counsyl.com)

REFERENCES

1. Stoll K, Resta R. Considering the cost of expanded carrier screening panels. *Genet Med* 2013;15:318–319.
2. Wilson JM, Jungner YG. *Principles and Practice of Screening for Disease*. World Health Organization: Geneva, 1968.
3. Dietz HC. New therapeutic approaches to mendelian disorders. *N Engl J Med* 2010;363:852–863.
4. Lewis C, Skirton H, Jones R. Can we make assumptions about the psychosocial impact of living as a carrier, based on studies assessing the effects of carrier testing? *J Genet Couns* 2011;20:80–97.

doi:10.1038/gim.2013.19



This work is licensed under a Creative Commons Attribution-NonCommercial-No Derivative Works 3.0 License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0/>