intervals: distal 16p11.2 deletions, 100%; proximal 16p11.2 deletions, 84.1%; and distal 1q21.1 deletions, 56.7%. However, these are likely overestimates, given that the controls were adults, and pediatric disease is likely to be underrepresented in that population.

Dr Benn raises concerns about falsely attributing disease causation to CNVs. Our calculations are based on the assumption that the CNV is contributory in all cases in which it is identified. As models for disease causation are shifting toward interaction of multiple genetic changes, including CNVs,[7] we believe this to be an acceptable assumption. Furthermore, by examining only CNVs with enrichment in cases, we ensure that we are not falsely attributing causation. Finally, we have excluded prenatal cases from our data to ensure that our testing population is made up exclusively of individuals with known abnormal phenotypes.

We thank Dr Benn for discussing some limitations of our estimates. There is some degree of uncertainty in our estimates, and it is important to keep that in mind when counseling. However, we believe that our 5% estimate for disease frequency is a more reasonable approximation than 1%. Furthermore, it is common to quote a background risk to expectant parents of 3–5% for a child with congenital anomalies, developmental delay, or intellectual disabilities.[8] If the counseling session includes framing the problem in terms of the high end of that estimate, then these penetrance estimates could be useful. For example, upon the identification of a 15q11.2 deletion, a couple could be counseled that this may double the chance of the child having congenital anomalies, developmental delay, or intellectual disabilities, changing the risk from the 5% background risk to closer to 10%.

DISCLOSURE

J.A.R. is an employee of Signature Genomic Laboratories, a subsidiary of PerkinElmer. E.E.E. is on the scientific advisory boards for Pacific Biosciences, SynapDx, and DNAnexus. The other authors declare no conflict of interest.

Jill A. Rosenfeld, MS[1], Bradley P. Coe, PhD[2], Evan E. Eichler, PhD[2,3], Howard Cuckle, DPhil[4] and Lisa G. Shaffer, PhD[5]

[1]Signature Genomic Laboratories, PerkinElmer, Inc., Spokane, Washington, USA; [2]Department of Genome Sciences, University of Washington, Seattle, Washington, USA; [3]Howard Hughes Medical Institute, University of Washington, Seattle, Washington, USA; [4]Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, New York, USA; [5]Paw Print Genetics, Genetic Veterinary Sciences, Inc., Spokane, Washington, USA. Correspondence: Jill A. Rosenfeld (rosenfeld@signaturegenomics.com)

REFERENCES

1. Benn PA. Prenatal counseling and the detection of copy-number variants. *Genet Med* 2013;15:316–317.
2. Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. Estimates of penetrance for recurrent pathogenic copy-number variations. *Genet Med* (2012); e-pub ahead of print 20 December 2012.
3. Baird PA, Anderson TW, Newcombe HB, Lowry RB. Genetic disorders in children and young adults: a population study. *Am J Hum Genet* 1988;42:677–693.
4. Strømme P, Bjørnstad PG, Ramstad K. Prevalence estimation of Williams syndrome. *J Child Neurol* 2002;17:269–271.
5. Elsea SH, Girirajan S. Smith-Magenis syndrome. *Eur J Hum Genet* 2008;16:412–421.
6. Vassos E, Collier DA, Holden S, et al. Penetrance for copy number variants associated with schizophrenia. *Hum Mol Genet* 2010;19:3477–3481.
7. Girirajan S, Rosenfeld JA, Coe BP, et al. Phenotypic heterogeneity of genomic disorders and rare copy-number variants. *N Engl J Med* 2012;367:1321–1331.
8. Harper PS. *Practical Genetic Counselling, 6th ed*. Arnold: London, 2004.

doi:10.1038/gim.2013.20

Considering the cost of expanded carrier screening panels

To the Editor: We write in reference to the article titled "An Empirical Estimate of Carrier Frequencies for 400+ Causal Mendelian Variants: Results From an Ethnically Diverse Clinical Sample of 23,453 Individuals" by Lazarin et al.[1]

We agree that ancestry-based carrier screening has significant drawbacks and may result in inequitable distribution of genetic testing and services. However, there are other issues to consider about carrier panels and the authors' recommendations, some of which the authors briefly mention at the end of their Discussion.

Expanded carrier screening panels are often marketed directly to patients and have been increasingly adopted into clinical practice despite the lack of supportive clinical guidelines. Expanded screening does not meet all of the generally accepted criteria for population screening. For example, many of the included conditions do not cause significant health impairment, have highly variable clinical courses, and/or are at low frequency in all populations, regardless of ancestry.

The authors imply that the low cost of multigene panels is one reason to support this practice, but the true costs of expanded carrier testing need to be carefully examined. The assay described in this article tests for up to 417 mutations that have been associated with 108 conditions. The authors state that for the purpose of this study, only the most clinically significant 96 conditions were evaluated. The sensitivity for individual carrier detection is reported to be <10% for about one-quarter of the screened conditions; fewer than one-half have a carrier detection rate >50%. Given the poor sensitivity of the panel for many of the included conditions, follow-up testing of the reproductive partner may involve more extensive genetic testing such as whole-gene sequencing, which currently costs several hundred to thousands of dollars per gene. This is not a trivial concern because about one in four individuals will prove to be a carrier for at least one disorder.

The time investment for follow-up counseling and risk assessment should also be factored into follow-up studies evaluating the true cost of expanded carrier testing. The psychosocial impact of this expanded screening both in the short and long

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, MS[1] and Robert Resta, MS[2]

[1]Department of Obstetrics and Gynecology, Madigan Healthcare System, Tacoma, Washington, USA; [2]Swedish 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 Resta[1] 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.