Table 1 Probability of an abnormal outcome when there is a 4% risk for a disorder unrelated to those detectable by microarray (type A) and a 1% birth incidence of a disorder that could be associated with a CNV (type B)

CNV present	*P*(type A)	*P*(type B)[a]	Total risk: *P*(A or B)	Probability based on Rosenfeld et al.[2]
Distal 16p11.2 deletion	0.04	0.24	0.28	0.62
15q11.2 Deletion	0.04	0.02	0.06	0.10

CNV, copy-number variation.

[a]Probability of disease, given the presence of the CNV, $P(G|D) = \frac{P(G|D)\,P(D)}{P(G|D)\,P(D) + P(G|\bar{D})\,P(\bar{D})}$ where

$P(G|D)$ = probability of CNV given type B disease; P(D) = probability of type B disease = 0.01; $P(G|\bar{D})$ = probability of CNV given no type B disease; $P(\bar{D})$ = probability of no type B disease = 0.99.

DNA tests and/or ultrasound and to provide reassurance following other screening. For many women, the presentation of a finding of a CNV of uncertain clinical significance may be very unhelpful. The challenge posed by using microarray testing needs to be met through enhanced professional education about the strengths and limitations of the testing, individualized counseling of women considering the test, and guidance on test utilization and interpretation from professional groups such as the American College of Medical Genetics and Genomics.

DISCLOSURE

The author declares no conflict of interest.

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doi:10.1038/gim.2013.16

Response to Benn

To the Editor: We thank Dr Benn for his letter titled "Prenatal Counseling and the Detection of Copy-Number Variants"[1] and agree that prenatal testing for copy-number variations (CNVs) differs from karyotyping, in which, more frequently, the patient can be given a clearer phenotypic expectation. Clarifying uncertainty is why we have attempted to estimate penetrance by including a wide range of possible associated disorders.[2] We also agree that prenatal microarray testing should be performed in the context of careful thought and counseling. Unclear results can be found regardless of careful use of the test, and our estimates provide one tool to aid counseling in such situations.

To obtain valid estimates for penetrance from CNV frequencies, it is important to know the fraction of the population with an abnormal phenotype that results in being referred for microarray testing. Our assumption that this fraction is approximately equal to the frequency of pediatric conditions with a genetic component—5% in a Canadian epidemiological study[3]—has some limitations, as pointed out by Dr Benn. Certain conditions may be diagnosed without microarray testing, although the rate of single-gene disorders in the Canadian study was only 0.36%.[3] Moreover, a subset of individuals with those conditions may still be referred for microarray testing, including individuals with conditions that can be caused by microdeletions (e.g., neurofibromatosis and cystic kidneys) or individuals who have atypical presentations of their diagnosed condition, for which clinicians wish to rule out other genetic factors altering the phenotype. Certain multifactorial conditions, if isolated, may not be a sufficient cause for microarray testing but are frequently part of syndromic presentations in individuals who are referred for microarray testing. Microarray testing may also be performed in a subset of individuals who have a condition, such as fetal alcohol syndrome, that does not have a genetic component, because it is important to rule out genetic causes before attributing their phenotypes to teratogens. Overall, although this raises the possibility that the 5% frequency may be an overestimate, further analysis of our data does not support Dr Benn's suggested reduction to 1%. For example, if we compare the population frequencies of known genetic syndromes such as Williams syndrome and Smith–Magenis syndrome due to microdeletions (1/7,500[4] and 0.9/15,000,[5] respectively) with the frequencies of these deletions in our patient population (110/48,637 and 46/48,637, respectively), it suggests that our testing population comes from a 6% subset of the population with abnormal phenotypes. This may be considered an upper limit, given that we may be underascertaining these syndromes if some cases are diagnosed through other methods such as fluorescence *in situ* hybridization. Finally, as Dr Benn points out, factors contributing to disease have likely changed since the Canadian study. Some conditions, like autism, are on the rise and may help to counterbalance the subset of the 5% that are not being tested by microarray.

As we state in our original report,[2] the controls used are not known to be disease free, and this can cause underestimation of penetrance. If we recalculate penetrance assuming controls are completely unscreened (having a probability of disease (P(D)) of 0.0512), as described in the supplemental methods by Vassos et al.,[6] the three CNVs with the highest penetrances have new estimates that are outside of their original confidence

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.

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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