they are "sick" or "healthy." Decision making in the context of illness likely influences the weightings given to risks and benefits—perhaps even reframing the balance of promise and concern entirely (a "game changer"). The authors were correct that for "most people" at this time, it does seem an absurd test. *Any* medical test would be absurd for most (healthy) people at any given time. But for those who benefit from the early days of a newer technology, the absurd becomes transformative.

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DISCLOSURE

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Response to Strong

To the Editor: We read with interest the letter by Drs Strong et al.[1] about our op-ed piece in the *Los Angeles Times*, but we stand by our statement that "for most people…whole genome sequencing is an absurd medical test."[2]

We agree with Dr Strong and colleagues that some patients can benefit from whole-genome or -exome sequencing—notably, individuals with rare phenotypes of likely genetic origin for whom conventional testing has been noninformative. Recent studies confirm that exome testing increases the number of patients in this group who receive a genetic diagnosis. However, the finding needs to be put in perspective; such patients are very rare.

Perhaps more important, the value of whole-genome sequencing for this purpose is likely to be short-term because comprehensive sequencing is now serving a discovery purpose. As the genetic etiology of rare conditions is clarified, these patients will be better served by targeted gene panels based on what we are now learning, because it is always preferable to avoid generating large amounts of potentially distracting additional data when addressing a focused clinical question.[3]

Much the same can be said for the other promising use of whole-genome sequencing: analyzing somatic changes in cancer tissues to inform therapy. The value of comprehensive sequencing in oncology is uncertain, but now this approach also serves a discovery purpose. Ultimately, the number of genes that provide useful information for cancer therapy will be finite and, again, most patients will be better served by targeted panels.

Thus while there may be some patients for whom whole-genome sequencing continues to be valuable, the number is likely to shrink over time as our knowledge accumulates.

Yet the public discourse about whole-genome sequencing suggests something very different: that the information will have universal value as a guide to individualized health care. Our commentary in the *Los Angeles Times* was motivated by the misleading nature of this discourse and the dangers that flow from it.

A person's genome is not only an ineffectual way to predict risk for most diseases but also a potential source of confusion and misdirection. First, as we noted, the noise-to-signal ratio is not merely high, it is astronomical. In short, for the general public it is a recipe for a lot of false alarms. Second, many quantitatively accurate genetic risks tend to be misleading because their effects are small relative to the contribution of a myriad of social and environmental factors.[4] A recent large cohort study demonstrated this nicely in type 2 diabetes; the effect of a genetic risk profile could be measured but was trivial compared with the effect of body weight.[5] In fact, the study suggested that a genetic risk profile would produce inaccurate information, underestimating diabetes risk in many overweight and obese people and overestimating it in many people with normal body weight.

Finally, we also agree with Dr Strong and colleagues that "*Any* medical test would be absurd for most (healthy) people at any given time." Unfortunately, that is how this particular test is being promoted. Geneticists have a responsibility to present genomic technology to the public in a more balanced fashion. Exaggerating the benefit of whole-genome sequencing, particularly as a useful test for most people, amounts to making a promise we cannot keep. Worse, it will lead to harm if people believe it.

DISCLOSURE

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Haploinsufficiency of the *MYT1L* gene causes intellectual disability frequently associated with behavioral disorder

To the Editor: We read with great interest the research article by De Rocker et al.[1] on the *MYT1L* gene and its role in intellectual disability (ID). Based on a series of 22 patients with different aberrations affecting this gene (deletions, mutations, and partial duplications), the authors describe the main clinical features associated with *MYT1L* haploinsufficiency as ID (22/22), speech delay (22/22), behavioral problems (19/22), and overweight (17/19). Apart from duplications, whose consequences may differ depending on their position, orientation, and other factors, only four of these patients present alterations affecting the *MYT1L* gene exclusively : two de novo point mutations and two de novo deletions. To contribute to this description, we would like to add one patient with a de novo intragenic deletion of *MYT1L* detected by comparative genomic hybridization array (arr(hg19) 2p25.3(1,843,177x2,1,844,493-1,983,593x1,2,000,941x2)dn).

Our patient is the first daughter of an unrelated healthy couple; the girl was born at 40 weeks of gestation via a natural delivery and had a birth weight of 2,700 g (10th to 25th percentile) and neonatal hypotonia. At the time of examination (at 4.5 years of age), she weighed 18 kg (50th percentile), was 109 cm tall (90th percentile), and presented microcephaly. Neurologically, she presented psychomotor developmental delay; she walked at 31 months and spoke her first words at 18 months, she does not control her sphincters overnight, and she attends a special education center. Behavioral problems fit those of autistic spectrum disorders (aggressiveness toward others, avoidance of eye contact, echolalia, hand and oral stereotypies, and hyperactivity). She also shows convergent strabismus, myopia, recurrent otitis, and seizures.

In relation to the association of *MYT1L* alteration with obesity proposed by De Rocker et al.,[1] our patient, with a weight in the normal range (50th percentile) in spite of a height in the 90th percentile (body mass index of 15.5 kg/m^2), does not fit this criterion. Although overweight in patients with *MYT1L* haploinsufficiency was previously described as an early-onset feature,[2] we cannot reject the possibility that our patient will develop obesity in late childhood, as occurs in other patients.[1] On the other hand, taking into account the World Health Organization definition of overweight and obesity based on both weight and body mass index,[3] it is remarkable that of the four patients with alteration affecting exclusively *MYT1L* who were described by De Rocker et al.,[1] only patient 10, with a body mass index > 30 kg/m^2, strictly meets these criteria.

Conversely, behavioral problems in our patient are strikingly similar to those reported by De Rocker et al,[1] including hyperactivity, aggressiveness toward others, avoidance of eye contact, echolalia, and hand and oral stereotypies. It is also of interest that, in addition to the two DECIPHER database–identified patients mentioned in the article (nos. 314 and 141), a third patient (255731) with a 0.47-Mb deletion affecting exclusively *MYT1L* has ID and autism as the only clinical descriptors.

More patients would be needed to better characterize the resulting phenotype, but, given the clinical similarities between patients with deletion or point mutation of the *MYT1L* gene, it is becoming clear that haploinsufficiency of this gene causes ID frequently associated with behavioral disorders.

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