dominant disorders—about 50% of apparently null variants are associated with an abnormal phenotype.[7] In addition, there are dozens of other rare variants in this gene, all of which are unlikely to be benign. Were many of these *PYGM* variants to be pathogenic, it would raise the estimate further, which seems incredible to us.

Clearly, we have a great deal to learn about the genetics, biology, and phenotypic consequences of mutations in *PYGM*. The letter by Nogales-Gadea et al.[1] amplifies and extends our work and underscores the utility of genomics in improving our understanding of the full spectrum of variation. We are grateful for their thoughtful critique and hope that we will have the opportunity to further benefit from their leadership and experience in elucidating this important and fascinating disorder.

DISCLOSURE

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In sickness and in health: context matters when considering potential benefits and risks of genome-wide sequencing

To the Editor: A recent op-ed piece in the *Los Angeles Times* characterized whole-genome sequencing (WGS) as "an absurd medical test."[1] The article focused on the deficiencies of WGS in identifying useful disease-risk associations, arguing that associations that are actionable are already identifiable through observed family history, and that beyond these "low hanging fruit" WGS is likely to do more harm than good.

Caution regarding the overstatement of benefits is warranted. However, the type of characterization of WGS offered in this article does a disservice to those for whom WGS is already useful. Broad statements proclaiming harm are similarly problematic to those of promise; such simplistic messages are misleading. The type of cautions (and potential benefits) directly relevant for a seemingly healthy person are likely different—or at least weighted differently—than for someone considering sequencing in the context of an undiagnosed disease or life-threatening illness. Context matters *a lot* when considering the potential risks and benefits of genome sequencing. Failure to account for the salience of context itself has far-reaching potential for harm.

Considerations regarding whether to pursue technologies, interventions, and treatment options are inherently context-dependent throughout medicine. Genome-wide sequencing is not any different in that regard. Ethical and legal experts commonly cite implications for long-term care and disability insurance as a significant risk of undergoing WGS or other types of next-generation sequencing. For a person diagnosed with a life-threatening illness, however, this risk has already been realized independent of testing. To forgo potentially beneficial therapy information in order to avoid this contextually irrelevant risk would be imprudent. Similarly, concerns related to potential psychosocial harms derived from learning about worrisome predispositional genes may no longer carry much weight for a person already experiencing an actual life-threatening illness.

The authors of the op-ed piece seem to focus on the use of WGS for preventive screening purposes and note the potential for misinterpretation of such results. For example, they specifically cite the irrelevance of a small increase in risk for health management or other interventions, which could result in unnecessary worry. This, however, is hardly the only use of WGS at this time. Nonscreening uses of WGS have already shown far more concrete applicability such as when genome-wide sequencing is proposed to end a diagnostic odyssey or guide chemotherapy. In these cases, testing has been done not to "predict the future" but rather to provide an actual diagnosis[2,3] or data to inform therapy best suited to an individual.[4]

Delineating the different contextual risks and benefits of WGS will take time and requires empirical exploration. One seemingly obvious but often neglected differentiation is the starting point for individuals (or family members), whether

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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