notably patients' physical activity habits, explain the individual variability in the phenotype manifestation of a common muscle defect as total myophosphorylase deficiency. Patients who exercise regularly—ideally under careful professional supervision—are much more likely to be less affected over the years. The beneficial muscle biological adaptations to regular exercise (increased oxidative capacity or muscle mass and power, among others) are likely to compensate, at least during nonstrenuous activities, for the inherited blockade in glycogenolysis.[2]

Finally, the next-generation sequencing approach proposed by De Castro et al.[1] is also important in that it might allow identification of *PYGM* polymorphisms, which have been largely uncovered in this disease, as we recently said in a review.[3] Publication of the polymorphisms discovered by the authors is potentially of great utility and in fact acknowledged by those who treat McArdle patients.

DISCLOSURE

The authors declare no conflict of interest.

Gisela Nogales-Gadea, PhD[1], Tomàs Pinós, PhD[2,3], Antoni L. Andreu, MD, PhD[2,3], Miguel A. Martín, PhD[3–5], Joaquin Arenas, PhD[4,5], and Alejandro Lucia, MD, PhD[5,6]

[1]Department of Neurosciences, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol I Campus Can Ruti, Universitat Autònoma de Barcelona, Badalona, Spain; [2]Departament de Patologia Mitocondrial i Neuromuscular, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autónoma de Barcelona, Barcelona, Spain; [3]Centre for Biomedical Network Research on Rare Diseases, Instituto de Salud Carlos III, Madrid, Spain; [4]Laboratorio de Enfermedades Mitocondriales y Neuromusculares. Hospital 12 de Octubre, Madrid, Spain; [5]Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain; [6]Universidad Europea, Madrid, Spain. Correspondence: Gisela Nogales-Gadea (gnogales@igtp.cat)

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Response to Nogales-Gadea *et al.*

To the Editor: In their letter, Nogales-Gadea et al.[1] present a thoughtful analysis of several points from our recently published paper entitled "Determining the Prevalence of McArdle Disease From Gene Frequency by Analysis of Next-Generation Sequencing Data."[2] The main thrust of our paper is that McArdle disease is more common than currently appreciated. Overall, Nogales-Gadea et al.[1] agreed with our conclusion, if not taking it even further, but they differed on the weighting of some of our explanations for why it may be underrecognized. These interesting and important questions are worthy of further discussion.

Nogales-Gadea et al.[1] agree that one explanation for our finding is that an unknown, but significant, proportion of patients are undiagnosed by virtue of having mild or no symptoms, which could be due to the intrinsic biology of the disorder or because the level of physical activity of many individuals with biallelic mutations in *PYGM* is not sufficient to trigger development of recognizable manifestations. We fully agree with this and believe that the penetrance and expressivity of McArdle disease are complex questions that deserve further study.

In our paper, we showed several alternative calculations based on carrier frequency that led us to estimate that prevalence of McArdle disease was 1/7,650 to 1/80,478, which is lower than previously estimated (1/100,000). We thought that the high end of this range (1/7,650) was unlikely and suggested as one possible explanation that some variants reported as pathogenic may actually be benign, consistent with the findings of Bell et al.[3] Nogales-Gadea et al.[1] questioned this hypothesis. They have very recently reviewed *PYGM* mutations in McArdle disease, and they generously shared a draft manuscript with us to support our writing of this response.[4] We repeated our calculations, including all variants reported as pathogenic in their manuscript, using the European-American subset of the National Heart, Lung, and Blood Institute's Exome Sequencing Project data set. The result was a prevalence estimate for McArdle disease of about 1/6,000, more common than even the highest estimate in our paper. More accurately, we should say that this is the predicted prevalence of individuals who harbor biallelic pathogenic mutations in *PYGM*. Assuming this to be true, one must then explain why the prevalence of the McArdle phenotype appears to be so much lower than this. We and Nogales-Gadea et al.[1] invoke various explanations that relate to the penetrance and expressivity of this trait and believe that it can be considered a gene–environment interaction, for which sustained energetic exercise is the environmental exposure or trigger. The authors are surely correct when they suggest that sedentary individuals have a lower probability of manifesting symptoms that might lead to a diagnosis of McArdle disease. Another potential explanation is the existence of modifiers. These could be acting in *cis*, analogous to the c.350G>A p.Arg117His and poly-T tract (ref. 5) or in *trans*, analogous to variants in *DCTN4* (ref. 6), both of which modify the phenotype associated with mutations in *CFTR*.

We also agree with Nogales-Gadea et al.[1] that next-generation sequencing highlights other potentially interesting issues. We did not address in our manuscript the observation that European–American data sets contain a number of apparently null *PYGM* variants that have not been observed in patients with disease. We have demonstrated that—at least in autosomal

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

M.D.C. declares no conflict of interest. L.G.B. has a potential conflict of interest to declare, as he is an unpaid consultant to the Illumina Corporation. He also receives royalties from Genentech and Amgen, although those are not likely relevant to the topic of this paper.

Mauricio De Castro, MD[1] and Leslie G. Biesecker, MD[2]

[1]Medical Genetics, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA; [2]Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Betheseda, Maryland, USA. Correspondence: Mauricio De Castro (mauricio.decastro-pretelt@nih.gov)

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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