**Unpacking the concept of a genomic result**

Commentary on ‘*Genomic Contextualism: Shifting the Rhetoric of Genetic Exceptionalism*’ by Garrison *et al*.

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Garrison *et al.* highlight the ways in which the idiom of genetic exceptionalism has unhelpfully sculpted discussions around handling genomic ‘results’. They suggest that ethical debates relating to genomics often founder because they attempt to focus on what to do with genomic results before having agreed on their nature, neglecting the complexity inherent in deciding what, out of a multitude of possible outcomes, should form a result from a genomic test. They introduce ‘genomic contextualism’ as a way to facilitate useful discussion and research, acknowledging that genomic information has some ways in which it overlaps with other kinds of medical information, and some ways in which it is distinct. We draw on this concept to highlight a further issue that warrants greater consideration: the recognition that the clinical impact of genomic variants is context-dependent, and that this may impinge on whether and when they should be conceptualised as results.

Genomic tests can detect four to five million genetic variants per person (Auton *et al.* 2015), but the navigation process from this raw genomic data to meaningful results is often inconsistent and unclear. The detailed but unfocussed approach of genomic tests provides an opportunity to identify variants with a broad range of potential clinical implications, but what questions should be asked of raw genomic data in order to construct clinical results, and how confident do any potential answers need to be? Only a tiny proportion of the millions of variants trawled in genomic tests will diagnose or predict anything clearly. Most will have no clinical impact; some may slightly influence the risk of various diseases under certain circumstances; and some may appear alarming based on purely hypothetical evidence. The distillation of millions of variants into a meaningful result involves a filtering process, but as yet there is little consensus about where and how to set the filters. Seemingly minor changes in this filtering activity may have a major impact on what is communicated to a patient as the ‘result’ of their test, and hence on the clinical care for them and their family.

Advances in technology mean that detection of genetic variants is now easy and cheap, and whether a given variant is present or not is usually unambiguous. However, the clinical meaning of a variant for the person in whom it is identified is often heavily context-dependent or unknown. Further opportunities for controversy arise in that although a person’s genetic variants are mostly fixed over their life course, different results may be drawn from their genomic data over time, with different variants rising to prominence as new questions are asked of the same raw data. However, detection of variants and detection of ‘results’ is often conflated. The spectre of genetic exceptionalism has distracted from this problem by sabotaging attempts at nuanced discussion as to how we should understand genomic information, forcing a perspective that it must be either globally exceptional, or identical to other medical information. In contrast, genomic contextualism allows us to recognise potential complexity and the need to negotiate core principles regarding what might constitute a genomic result.

The context-dependence of variant significance is acknowledged in widely used international criteria for assessing genetic variants, which state that laboratories must evaluate variants ‘in the context of the patient’s and family’s history’ (Richards *et al*. 2015). However, this is easier said than done. Technical scientific parameters, such as variant rarity or predicted effect on protein structure, are much easier to categorise and legislate around than more abstract but crucial questions such as ‘what might this mean in the context of this person’s life?’ Nevertheless, the clinical significance of genomic variants is inherently context-dependent. For example, the common ΔF508 variant in the *CFTR* gene may cause cystic fibrosis in one person, cause another person to have a child with cystic fibrosis or, for another person, have no impact at all. Other genetic factors (such as the presence or absence of another disease-causing *CFTR* variant in a person or their partner) and social factors (such as a person’s position in a biological family) influence the impact that the variant has for a given individual. For example, the same variant would have different implications if identified in a 90-year-old with no living family, than if found in a 20-year-old planning a pregnancy. Could the presence of this same variant therefore constitute a result for one person but not for another?

How should we conceptualise variants whose impacts are context-dependent, but where it is uncertain whether the relevant context will ever arise? For example, people with an HLA-B\*5701 allele are at risk of a life-threatening reaction on repeated exposure to the antiretroviral drug abacavir (Mallal *et al.* 2008). If a genomic test detects HLA-B\*5701 in a newborn baby, should that be a ‘result’? They might need antiretroviral treatment at some point, so wouldn’t it be helpful to know? However, there are thousands of variants with potential to affect drug safety, and each person will only be prescribed a limited number of drugs during their lifetime. Some variants will affect how a person metabolises drugs that are yet to be discovered. One approach would be to check for and communicate genetic susceptibility to adverse reactions only when considering prescribing the relevant drug, but this highlights that the construction of a genomic result also relies on temporal factors: a variant may grow into a result depending on a person’s age or life events. However, if medical factors such as intention to prescribe have the power to transform a variant into a result, if there is no such intention, does this mean that the same variant would not constitute a result? If a clinician’s desire to know such information can cement a variant’s status as a result, can parental curiosity do the same? Who should define what constitutes a genomic result, and what should happen if different people have different views about how to conceptualise the same variant in the same person?

Additional complexity arises due to the familial nature of genetic information. Comparison of a patient’s genome with that of their biological relatives is often helpful in making diagnoses, but this draws people into genomic investigations who do not themselves have overt health problems, and who may not be aware that they may receive information from the test with relevance to their own health. Should variants identified in their genomic data be conceptualised differently to the variants identified in their unwell relative? Should a seemingly healthy person asked to provide a sample to assist interpretation of their family member’s genomic data get a result of their own? Would a result for their unwell relative also constitute a result for them, if their contribution of genomic data made its identification possible?

We have highlighted various contextual factors that may impinge on whether a given genomic variant is perceived as a result, including genetic background, temporal factors, and a person’s position in a biological family. However, some factors impacting interpretation of genomic variation are less easy to predict and negotiate around: for example, the issue that ostensibly the same genomic test may be interpreted differently depending on which laboratory it is sent to. Interpretation of genomic data is difficult, and sometimes there is no consensus as to whether particular variants are truly linked to disease. A recent study comparing variant classification between nine genetic laboratories found that, although they all used the same classification guidelines, only 34% of variants were given the same classification by all laboratories, and 22% were classified so differently that it might affect medical care (Amendola *et al.* 2016). Whilst this may seem like a technical issue, it has profound implications for patients and families: relatives living in different areas may have genomic testing aiming to answer the same clinical question, but the same variant identified in both may be communicated as a ‘result’ to one but not to the other.

How genomic information should be understood is not clear, yet how we perceive it underpins how we might conceptualise genomic results. It does seem evident that regardless of whether the technical scientific potential of any given genetic variant to cause disease is well known, the clinical impact of the variant will be to some extent context-dependent. Sometimes these contextual factors are well understood as we have outlined above, but often this is not the case. The concept of genomic contextualism outlined by Garrison *et al.* should facilitate research in this area, allowing us to take stock at a more fundamental level, considering what genomic results should be rather than how we should legislate around them. It sets the scene for progress by allowing questioning and argument as to whether and how particular genomic information should be constructed as genomic results, sidestepping concerns around genetic exceptionalism and allowing more nuanced comparison with results from other areas of medicine. In doing this, it highlights the need to research core questions: what is the nature of a genomic result, and how and when should we decide what it consists of?

**References**

Amendola, L. M., G. P. Jarvik, M. C. Leo, H. M. McLaughlin, Y. Akkari, M. D. Amaral, J. S. Berg, S. Biswas, K. M. Bowling, L. K. Conlin, G. M. Cooper, M. O. Dorschner, M. C. Dulik, A. A. Ghazani, R. Ghosh, R. C. Green, R. Hart, C. Horton, J. J. Johnston, M. S. Lebo, A. Milosavljevic, J. Ou, C. M. Pak, R. Y. Patel, S. Punj, C. S. Richards, J. Salama, N. T. Strande, Y. Yang, S. E. Plon, L. G. Biesecker, and H. L. Rehm. 2016. "Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium." *American Journal of Human Genetics* 99 (1):247. doi: 10.1016/j.ajhg.2016.06.001.

Auton, A., L. D. Brooks, R. M. Durbin, E. P. Garrison, H. M. Kang, J. O. Korbel, J. L. Marchini, S. McCarthy, G. A. McVean, G. R. Abecasis, and 1000 Genomes Project Consortium. 2015. "A global reference for human genetic variation." *Nature* 526 (7571):68-74. doi: 10.1038/nature15393.

Mallal, S., E. Phillips, G. Carosi, J. M. Molina, C. Workman, J. Tomazic, E. Jägel-Guedes, S. Rugina, O. Kozyrev, J. F. Cid, P. Hay, D. Nolan, S. Hughes, A. Hughes, S. Ryan, N. Fitch, D. Thorborn, A. Benbow, and PREDICT-1 Study Team. 2008. "HLA-B\*5701 screening for hypersensitivity to abacavir." *New England Journal of Medicine* 358 (6):568-79. doi: 10.1056/NEJMoa0706135.

Richards, S., N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H. L. Rehm, and ACMG Laboratory Quality Assurance Committee. 2015. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in Medicine* 17 (5):405-24. doi: 10.1038/gim.2015.30.