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ARTICLE

What is the meaning of a 'genomic result' in the context of pregnancy?

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Abstract

Prenatal genetic testing and analysis in the past was usually only offered when a particular fetal phenotype was noted or suspected, meaning that filtering and interpretation of genetic variants identified could be anchored in attempts to explain an existing health concern. Advanced genomic testing is now increasingly used in "low-risk" pregnancies, producing information on genotype adrift of the phenotypic data that is necessary to give it meaning, thus increasing the difficulty in predicting whether and how particular genetic variants might affect future development and health. A challenge to healthcare scientists, clinicians, and parents therefore is deciding what qualities prenatal genotypic variation should have in order to be constructed as a 'result.' At the same time, such tests are often re requested in order to make binary decisions about whether to continue a pregnancy or not. As a range of professional organizations develop guidelines on the use of advanced genomic testing during pregnancy, we highlight the particular difficulties of discovering ambiguous findings such as variants with uncertain clinical significance, susceptibility loci for neurodevelopmental problems and susceptibility to adult-onset diseases. We aim to foster international discussions about how decisions around disclosure are made and how uncertainty is communicated.

Introduction

Constructing genomic results in the context of pregnancy is particularly challenging as the data they are developed from often convey rather uncertain information but are nevertheless the substrate for a very binary decision—whether to continue a pregnancy or not. Public discourse around genomic technology tends to portray all genomic information as meaningful yet advanced genomic tests often produce vast quantities of uncertain or probabilistic data. Unsurprisingly, some prospective parents express a wish to know 'everything' from prenatal genetic and genomic tests [1] yet communicating this can clash uncomfortably with the dichotomy of the decision driven by such findings. Recent years have seen increasing use of advanced genomic testing in uneventful or low-risk pregnancies [2], producing information on genotype adrift of the phenotypic data that is often necessary to give it meaning. This greatly increases the difficulty in predicting whether and how particular genetic variants might affect future development and health and presents a challenge to scientists, clinicians, and parents in deciding what qualities prenatal genotypic variation should have in order to be constructed as a 'result.'

Genomics in a prenatal context

Attempts to predict the future health of a fetus are inevitably coarse. Any pregnancy involves uncertainty: for any pregnancy that continues to term there will be a 2–3% chance that the resultant child will have a 'birth defect' [3]; a 50% chance they will develop cancer at some point in their lifetime [4]; a 33% chance they will experience mental health problems [5] and a 25% chance they will die from cardiovascular disease [6].

Tests carried out during pregnancy, such as fetal ultrasound, might delineate, say, a structural brain anomaly, but whether this will have any functional consequences may be

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unclear [7], and the resulting uncertainty or anxiety has the potential to persist for many years after a child is born. Additional investigations may be offered in pursuit of clarity, for example fetal MRI, or genomic testing, but often the future of the fetus will remain opaque [8]. Furthermore, many potential fetal phenotypes will be difficult or impossible to assess in the prenatal period, for example intellectual disability.

Genomic tests generate a slew of data, and plucking out meaningful results is no simple task. For example, each person has around 100,000 rare genetic variants in their genome [9]; most of these will have very little effect on health, but many will appear concerning based on purely hypothetical evidence [10]. This opens up questions as to what qualities genetic variants should have in order be considered meaningful results in the prenatal context, and then whether there is different meaning in pregnancies in which an abnormality is already suspected.

The challenge of constructing a result from genomic data is not unique to pregnancy, but with limited opportunity to assess phenotype, and curtailed time for decision-making, the prenatal context intensifies the pressure on making decisions regarding which genetic variants to value as clinical results: what nature, magnitude, and certainty of risk might they need to confer? This complexity is reflected in the wide variation in clinical practice between different centers and countries: policies range from tending to disclose a wide range of findings, including genetic variants with uncertain or adult-onset impacts [11], to disclosing only variants with well-established, childhood-onset clinical consequences [12, 13]. What factors should determine whether and when a particular genomic variant is valued as a meaningful result (e.g., magnitude, and certainty of risk) and who should be involved in these decisions? The landscape to which these questions apply is shifting both as the genetic tests on offer become broader in scope, and as they increasingly detach from being used only in 'high-risk' contexts where they sought to explain or clarify existing clinical problems, to being used in 'low-risk' pregnancies where there is (at least initially) no clinical concern to explore. Testing in 'low-risk' pregnancies may be offered routinely to all pregnant women if noninvasive genomic testing—that does not have the associated miscarriage risks of older invasive investigations—becomes more accessible through improved sensitivity and lower costs.

The nuanced nature of genomic results

The main prenatal investigations in current use are chromosomal microarray analysis (CMA), which checks for missing or extra genomic material, and exome-sequencing (ES), which identifies variants in the coding sequence of the genome. CMA is offered as a first-line test in pregnancies with structural anomalies [14], and ES is gradually being offered in pregnancies with structural anomalies and normal CMA [15]. Most CMAs and ESs will be 'normal,' but some will establish comparatively clear-cut diagnoses. As tests interrogate progressively more of the genetic code at ever-higher resolution, they exponentially increase the chance of finding genetic variants with uncertain or unexpected implications [16].

Although uncertain genomic variants have in common the inability to define in pregnancy the exact phenotype of the child once born, there are unique aspects to various types of uncertain information.

Variants of uncertain significance

Variants of unknown/uncertain clinical significance (VUS) are genetic variations that have conflicting evidence of pathogenicity based on various bioinformatic tools, or no data at all. Obtaining greater phenotypic detail can assist in the interpretation of these variants, yet is often difficult in pregnancy where not all phenotypes can be readily identified (e.g., intellectual disability). Establishing whether a variant is inherited or *de novo* may sometimes assist interpretation, yet due to the possibility of variable expression/penetrance, inherited variants cannot automatically be classified as benign [17, 18]. In time, with growing evidence, it is likely that the majority of VUS could be classified as pathogenic (playing a part in disease causation) or benign [19]. Yet in the context of a current pregnancy, the hope of future clarification cannot help decision-making. Nevertheless, classification might be achieved prior to the next pregnancy, which could be helpful for parents on the one hand, but could be emotionally challenging on the other hand, especially if, based on the eventual classification, parents might have made a different decision about their earlier pregnancy.

Susceptibility loci

Susceptibility loci (SL) are recurrent copy-number variants (CNVs) identified via CMA with incomplete penetrance and variable phenotype, often associated with neurodevelopmental problems [20]. The spectrum of effects of an SL may be well understood, but there is no way to know whether a given fetus will experience any of the difficulties associated. For SL, unlike VUS, uncertainty centers around whether a genetic variation will cause disease in a particular person, rather than whether the variation is associated with disease at all. SL are often inherited from a healthy parent, in which case there would be a 50% chance of similar inheritance in each pregnancy. SL can explain part of the etiology of the associated disorder(s) but other genetic and

nongenetic events are likely required in order for associated clinical features to manifest. The more common SL are those with low penetrance, meaning the majority of individual carrying the SL will never go onto develop associated symptoms [20]. Single-nucleotide variants (SNVs) identified via ES can also be associated with low penetrance and variable expression inviting us to reflect on at what point penetrance is sufficiently low that it is no longer appropriate to consider an SL/low-penetrance SNV to constitute a prenatal result.

Predisposition to adult-onset conditions

Another challenging finding is a genetic variation associated with risks for adult-onset conditions. For example, finding that a fetus would have an increased risk of breast cancer from the third decade of life onwards [21]. In a postnatal setting, professional guidance suggests that children should not usually be tested for adult-onset conditions known in their families until they are old enough to decide for themselves whether they might want this information, even if their parents request it [22]. Should fetuses have similar protections against their parents finding out about possible health risks in their far future? Parents may express a strong interest in knowing such information, but what, if any, boundaries should be placed around what it is reasonable for them to know? In addition, what are legitimate responses by the clinical team if parents ask for a termination of the pregnancy based on such findings? For example, how much should clinicians press the point that such findings are rarely absolute and that they may predict a condition rather poorly, especially if there is no family history of it?

Genetic tendencies toward adult-onset conditions might of course have been inherited from a parent, so that if such findings in a fetus are constructed as a result, this might allow parents themselves to be made aware of and tested for a health risk at a point in their lives where screening or treatment might be beneficial. Such parents may already be aware of their inheritance, but finding this out will require a form of result construction in the fetus. Arguably, in pregnancies that continue, the fetus as a future person benefits if their genomic test contributes to safeguarding the health of their parents. To what extent should construction of prenatal genomic results be influenced by the timeframe within which identification of a risk is likely to lead to benefit, and to whom should this benefit apply?

The changing landscape around prenatal testing

Early prenatal tests sought to determine whether a fetus had inherited a genetic condition that had affected others in the family, for example cystic fibrosis or Tay-Sachs disease, or to check whether unusual features in a pregnancy might be explained by a major chromosomal anomaly. Whilst the results of such tests might leave prospective parents with difficult choices, there was usually a clear clinical indication for the test, and some certainty as to what the results might mean [23]. For such pregnancies, genomic testing will aim to give clarity: highly uncertain or tentative genotypic findings may be unhelpful, and vulnerable to being given greater weight than might be warranted from a technical scientific perspective, but the already identified clinical problem provides a lens through which to interpret the genomic data.

Interpretation of genomic data depends heavily on the clinical context (phenotype) in which it is acquired, but this nuance is often missing from public discussions about genetic and genomic tests. Advertising from direct-to-consumer genetic testing companies, and popular discourse around 'personalized medicine' and the genomic testing that underlies it, gives a pervasive message that genomic information is routinely clear-cut and useful, and that more data will mean more information, more power, and more choice [24, 25]. Such messages are also propagated by stakeholders with less direct commercial interests, for example, ongoing genomics research funding depends on society continuing to view the information it provides as valuable, and worthy of investment.

It is therefore unsurprising that some prospective parents might see prenatal genomic testing as a way to achieve certainty and/or reassurance as to the future of a pregnancy, regardless of whether there is a clinical problem to explain. In a survey of nearly 2000 adults in the UK, 'informative' was the most popular word chosen to describe genome sequencing in healthcare [26].

The growing availability of genomic testing, together with a very low miscarriage rate from invasive prenatal diagnosis [27–29], result in a demand for genomic tests in uneventful "low-risk" pregnancies [30, 31]. With the increasing sensitivity of noninvasive prenatal testing in identifying fetal sub-chromosomal CNVs [32] and SNVs [33–35], it is expected that the number of advanced genomic tests done in the context of uneventful pregnancies will continue to escalate. The chances of identifying variants with uncertain clinical significance and/or low-penetrant SL in these uneventful pregnancies will often be higher than the chance of identifying variants that would clearly have a severe impact on health in childhood [2].

Invasive prenatal tests cannot be done without health professional involvement, as specialist equipment and expertise are needed to obtain a sample for testing, embedding an opportunity for parents to discuss their expectations around prenatal testing with a clinician experienced in maternal and fetal medicine prior to undergoing a test. This is set to change with increasing use of

"noninvasive" prenatal testing—this only requires a maternal blood sample, which a patient could arrange to have taken and sent away to, for example, a direct-to-consumer genetic testing company, without crossing paths with a specialist. Whilst being able to offer prenatal tests without the risk of miscarriage is something to celebrate, there are risks that their technical safety will lead to people thinking of prenatal testing as 'risk-free' and routine. This may mean that more people have prenatal genomic testing without having thought in detail as to whether they truly want to know the information that it might provide, and perhaps without being aware that its outcome may be very uncertain [23, 36].

Decision-makers in prenatal genomic result construction

Navigating from millions of variants per person to clinical results requires filtering, interpretation and disclosure decisions. Well-established bioinformatic filtering pipelines, and variant interpretation guidelines such as the ACMG criteria [37], perform much of this curation, but in choosing a filtering pipeline, or considering which ACMG criteria apply, scientists and clinicians are already placed in the position of working out what sort of data should potentially be valued as a 'result.'

Over the last few decades, medicine has increasingly recognized the importance of involving patients in clinical decision-making, and acknowledging their expertise in terms of judging what way forward would be best in the context of their own lives. Clinical genetics has a long history of aspiring to non-directive counseling [38], where clinicians aim to provide a balanced view of a patient's options, but the patient determines how and whether to act on the information that they have been given. "Binning" models for communicating findings from genomic tests have been advocated as a potential way by which patients can make choices as to what sort of information they might want to know from a test, picking from menus of "preventable," "high risk," etc. [39]. However, these choices are often more ambiguous than they might appear—for example, different people might mean different things by an "actionable" finding [40], and might attribute different weight to the same numerical risk [41].

Capturing subtle differences as to what sort of genomic information parents might value as a result of testing, in such a way that professionals can use this as an unambiguous guide to interpreting their prenatal test, is next to impossible. Expecting deference to parental consent to easily and exclusively resolve any dilemma relating to construction of prenatal genomic results is therefore inappropriate, both relying on and feeding into an overly deterministic perspective on genomics (i.e., an expectation that genomic variation can be uncontroversially boxed into discrete categories with clear sequelae). Whilst in-depth consent conversations in advance of testing might give health professionals some idea of what a prenatal "result" might mean for particular parents, even where such conversations have happened, professionals are still left in the position of trying to apply principles discussed in abstract, to the genotypic data actually identified.

We argue that as a part of the consent process for prenatal genomic testing, it is essential to be explicit about the necessary involvement of scientists and clinicians in the process of interpreting data to produce genomic results. This is important both for maintaining trust by explaining why prenatal genomic results might sometimes be different in nature to what parents initially anticipated, and to avoid unfairly positioning parents as wholly carrying the burden of whatever result comes from their prenatal test, whether or not it bears any relation to what they were expecting, because "they asked for it" [42]. Perhaps the parental role in construction of genomic results in the prenatal setting could be seen as somewhat analogous to the birth plan a woman might develop regarding delivery—developing preferences, and establishing key information in advance are very important, and sometimes these preferences can then be followed to the letter. However, an evolving or unexpected situation might mean that a different course is more appropriate, and in order to achieve a good outcome, the woman and the professionals involved in her care need to depart from, or adapt, the original plan.

Conclusions

The clinical uncertainty and ambiguity of the information provided by many genomic tests is particularly glaring in the prenatal context. Popular discourse around genomic testing tends to present its results as clear-cut and informative, so many prospective parents may understandably express a wish to know "all the information," and yet be unprepared that this may be uncertain and probabilistic. We highlight that construction of a genomic result in the context of a particular pregnancy is an interpretative process—parental preference may guide and to some extent direct this process, but professionals will sometimes have to make choices as to how best to honor previously expressed parental preferences in situations involving ambiguity. We argue the need to be explicit about this as part of the consent process for prenatal genomic tests—caricaturing prenatal result construction as a simple matter of parental choice does a disservice both to the scientists and clinicians whose expertise is brought to bear in the process, but also to the parents, who may feel they were told they had choices that turned out to be illusory.

As prenatal genomic testing expands in technical scope and transitions to being offered in uneventful pregnancies, the need to explore what a prenatal genomic result should encompass, who should be involved in defining this, and how and to what extent parental preferences can meaningfully influence result construction, is becoming more urgent.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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