Genomic Variation: What Does It Mean?

Marian Reiff
Barbara A. Bernhardt
Surabhi Mulchandani

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Abstract
New technologies have given us the ability to detect genomic variation at resolutions 50-100 times greater than earlier tests. The good news is that we can now detect variations that help explain developmental delays, autism, or multiple congenital anomalies in up to 20% of children. The bad news is that we can also detect small missing or extra pieces of chromosomes that remain unexplained: that is, we don’t know whether they have any clinical significance at all. The rapid pace of technological change may have outpaced the lab’s ability to interpret, providers’ abilities to explain, and patients’ abilities to understand the test results. This Issue Brief summarizes a series of studies examining the uncertainties revolving around chromosomal microarray testing, which has become the new standard of practice in genetic testing of children with unexplained anomalies.

Keywords
medical technology, personalized medicine and genomics

Disciplines
Health Services Research | Medical Genetics

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Increasingly, geneticists, pediatricians and subspecialists are ordering CMA to diagnose children with unexplained neurodevelopmental delays. CMA can detect thousands of “copy number variants” throughout the genome, and yields a diagnosis three to five times more often than older methods of chromosome analysis. Finding a genetic diagnosis can often provide relief to families, target future medical care, facilitate access to educational interventions, and help parents understand the risk of recurrence in future offspring.

- In 2008, the American College of Medical Genetics recommended that CMA replace karyotyping as a first-line genetic test in infants and children, because of the test’s enhanced diagnostic abilities. CMA practice guidelines emphasize the importance of pre-test counseling and informed consent to ensure that families are prepared for the information, and can choose how much information to receive.
- Microarray testing results fall into three main categories: negative (no clinically significant variation), pathogenic (a variation known to result in a genetic condition), and “variant of unknown significance (VUS)”. On average, about 10% of CMA results fall into the last category.
- Many VUS results can be resolved by genetic testing of parents to determine whether a variant has been inherited or has arisen anew in the child. Although most variants inherited from a “normal” parent are assumed to be benign, it is possible that the parent has a very mild or unexpressed form of the child’s condition. Further, genetic testing of a parent or child may yield “incidental” findings not related to the reason for testing, such as a predisposition to develop Alzheimer disease.
Reiff and colleagues explored clinicians’ perspectives about ordering CMA and about effectively interpreting results and communicating with families. Forty clinicians who had ordered CMA answered an online survey and responded to a hypothetical case of uncertain and incidental findings in a parent.

- The clinicians had ordered CMA at least once from the Children’s Hospital of Philadelphia between May 2008 and March 2011. Respondents were general pediatricians (27.5%), medical geneticists (12.5%), and pediatric subspecialists (60%, including seven neonatologists, five neurologists, four endocrinologists, three developmental pediatricians, one hematologist, one gastroenterologist, one oncologist, one ophthalmologist, and one critical care specialist).
- Not surprisingly, comfort levels differed for explaining the three types of results, with the highest comfort levels for normal results and the lowest comfort levels for VUS results. Most non-geneticists reported that they would discuss a VUS finding with a genetic specialist.

From the parents’ perspective, a struggle for comprehension, meaning, and support

To explore how families understand and give meaning to the results of CMA testing, Reiff and colleagues interviewed 25 families, 11 of whom had received pathogenic results and 14 who had received VUS results. The investigators interviewed 31 parents (23 mothers and 8 fathers), either in-person or by telephone, whose children had undergone CMA testing at the Children’s Hospital of Philadelphia. In 17 families, the ordering physician was a geneticist; in the other eight families, a non-geneticist.

- Parents receiving both uncertain and pathogenic results said that they had trouble understanding the result initially (5 VUS and 5 pathogenic). Four reported that they received the results initially from non-genetics professionals lacking the expertise to provide adequate explanation. These misunderstandings were usually resolved eventually by discussion with genetics experts.
- Receiving results by telephone, long waits to see a geneticist to discuss the results, inconsistent information provided by different health professionals, and Internet searches based on inadequate or inaccurate information all contributed to difficulties in understanding the results.
- Many participants, even when they understood the results, still struggled to understand the meaning and potential implications of the results, and expressed a need for more information and explanation. A typical response was, “I understood what they told me, but I wish I could have found out more about what it meant.”
- Results were perceived to be helpful in providing a causal explanation (8 pathogenic and 5 VUS), and in anticipating the child’s future needs (4 pathogenic and 4 VUS). Many expressed relief at finding a causal explanation. However, a parent who found out that he had the same deletion as his child reported feeling shocked and subsequently questioning his sense of self.
- Most parents thought that the benefits of the test would become more apparent in the future, as more people are tested.
- Several respondents wanted to connect with other families with the same genetic variant as a potential source of emotional support. They expressed frustration that the hospital could not facilitate a connection with other parents because of privacy regulations.

From the clinicians’ perspective, a need for more education to explain and interpret results

- Our understanding of genomic variation is a rapidly moving target. Labs now routinely report new (de-identified) variations to public databases and publish clinical reports of novel findings. Thus, the interpretation of a VUS result may change over time as the worldwide knowledge base grows. Further, there is some variability in how different labs interpret different results.
These studies highlight key challenges in the practice of genomic medicine for patients, families, and clinicians. The increasing use of genetic sequencing technology will likely magnify these problems, as we will be able to quickly describe and detect all human genetic variation long before we understand what most of it means for the individual patient.

- Genetics expertise makes a big difference in how abnormal and uncertain results are delivered and received, and yet the current medical genetics workforce is not sufficient to meet this demand. Non-geneticists need educational resources to improve their ability to understand and communicate sometimes complex genetic findings.
POLICY IMPLICATIONS

Continued

- Similarly, families need educational resources and support before and after genetic testing. Given the limited number of genetics professionals, new strategies are needed to overcome long waits for genetic counseling and misinformed Internet searches. Parents who have been through the experience of receiving uncertain results may be the most available and underutilized resource for new families. Programs to train parents and facilitate referrals should be fostered.
- Both providers and patients need regularly updated resources that summarize what is currently known about the specific “copy number variants” reported to them.
- In addition to provider- and patient-level training and support, we should consider system-level interventions that improve the infrastructure for integrating genomic medicine into clinic care. Institutional policies should encourage compliance with best practice guidelines around ordering and explaining genetic test results. Electronic ordering systems and the electronic medical record provide opportunities to develop and test new, interactive ways of delivering genetics education and information in appropriate and timely formats to both clinicians and families.


This Issue Brief was supported by the National Human Genome Research Institute, Center for the Integration of Genetic Healthcare Technologies, University of Pennsylvania Perelman School of Medicine (P50HG004487).

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