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Genomic Variation: What Does It Mean?

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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.

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Genomic Variation: What Does It Mean?

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Editor's note: 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.

Chromosomal microarray analysis (CMA) replaces karyotyping as standard of care

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.

- 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.

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

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.

- Overall, non-geneticists reported a strong need for more education about interpreting and explaining CMA results. Most clinicians felt that parents' understanding of CMA results was somewhat low, although geneticists rated parent understanding higher than non-geneticists.
- While clinical guidelines recommend pre-test counseling to prepare families for incidental or uncertain findings, many clinicians did not consider it pertinent in pre-test counseling of parents to discuss the potential for CMA to uncover incidental findings. This varied by specialty: all general pediatricians felt it was pertinent, compared to 60% of geneticists and 39% of pediatric subspecialists.

Prenatal use of CMA poses even more challenges

Prenatal CMA has not yet supplanted karyotyping as the standard of care, but a newly published study has demonstrated its greater diagnostic yield. Prenatal use of CMA poses even more challenges because any indication of a problem with the fetus can transform the experience of pregnancy. To understand women's experiences, Bernhardt and colleagues interviewed 23 women who had both karyotyping and CMA as part of a large multicenter study, and had received either pathogenic or VUS results. Telephone interviews were conducted at least six month postpartum or post-pregnancy termination.

- All women had received genetic counseling and were undergoing an invasive prenatal diagnostic procedure (either amniocentesis or chorionic villus sampling) for karyotype analysis. During the informed consent session, a genetic counselor explained the risks, benefits, and limitations of CMA testing. All women received their results from the genetic counselor or a study obstetrician, with follow-up counseling available.
- Initially, receiving abnormal CMA results left most women shocked, anxious, confused, and overwhelmed. Many of those who had received abnormal CMA results after first receiving normal karyotyping results felt "blindsided." Many women discussed the difficulty of emotionally and intellectually managing the uncertainties of results given how far along they were in their pregnancies.
- The women needed support to manage, understand, and act on the CMA results. Most women reported receiving help from the study obstetrician or genetic counselor, although many commented that they wanted more support with decision-making about continuing or terminating the pregnancy.
- Most women understood that CMA could identify serious problems in the baby missed on routine cytogenetic analysis. But only one recalled being told that some results might be uncertain or uninterpretable. When given those results, many women considered this information to be knowledge they wished they did not have (toxic knowledge). Even after delivering a normal-appearing baby, 8 of the 16 women who continued their pregnancies had lingering worries about their child's development.

POLICY IMPLICATIONS

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.

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POLICY IMPLICATIONS
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- 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 is based on the following articles: B.A. Bernhardt, D. Soucier, K. Hanson, et al. Women's experiences receiving abnormal prenatal chromosomal array testing results. Genetics in Medicine, February 2013, vol. 15, pp. 139-145; M. Reiff, K. Ross, S. Mulchandani, et al. Physicians' perspectives on the uncertainties and implications of chromosomal microarray testing of children and families. Clinical Genetics, January 2013, vol. 83, pp. 23-30; M. Reiff, B.A. Bernhardt, S. Mulchandani, et al. "What does it mean?": Uncertainties in understanding results of chromosomal microarray testing. Genetics in Medicine, February 2012, vol. 14, pp. 250-258.

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