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Parents' Perceptions of the Usefulness of Chromosomal Microarray Analysis for Children with Autism Spectrum Disorders

Marian Reiff[1], **Ellen Giarelli**[2], **Barbara A. Bernhardt**[1], **Ebony Easley**[3], **Nancy B. Spinner**[4,5], **Pamela L. Sankar**[6], and **Surabhi Mulchandani**[4]

Marian Reiff: marian.reiff@uphs.upenn.edu

[1]Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[2]College of Nursing and Health Professions, Drexel University, Philadelphia, Pennsylvania

[3]Mixed Methods Research Lab, University of Pennsylvania, Philadelphia, Pennsylvania

[4]Division of Genomic Diagnostics and the Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[5]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[6]Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Clinical guidelines recommend chromosomal microarray analysis (CMA) for all children with autism spectrum disorders (ASDs). We explored the test's perceived usefulness among parents of children with ASD who had undergone CMA, and received a result categorized as pathogenic, variant of uncertain significance, or negative. Fifty-seven parents participated in a semi-structured telephone interview, and 50 also completed a survey. Most parents reported that CMA was helpful for their child and family. Major themes regarding perceived usefulness were: medical care, educational and behavioral interventions, causal explanation, information for family members, and advancing knowledge. Limits to utility, uncertainties and negative outcomes were also identified. Our findings highlight the importance of considering both health and non-health related utility in genomic testing.

Keywords

Autism spectrum disorders; Chromosomal microarray analysis; Genomic testing; Qualitative; Perceived utility; Parent perspectives

Correspondence to: Marian Reiff, marian.reiff@uphs.upenn.edu.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

Introduction

The ability to detect genetic causation for autism spectrum disorder (ASD) has improved due to the use of genome wide screening technologies such as chromosomal microarray analysis (CMA) to search for copy number variants (CNVs), and next generation sequencing for single nucleotide variation (Shen and Miller 2014; Talkowski et al. 2014; Veenstra-VanderWeele et al. 2004). Genetic testing is not considered a diagnostic test for ASD, however, several studies have demonstrated the clinical utility of CMA in terms of changes in clinical management and medical care (Agency for Healthcare Research and Quality (AHRQ) 2014; Beaudet 2013; Coulter et al. 2011; Ellison et al. 2012; Hayeems et al. 2014; Henderson et al. 2014; Mefford et al. 2012; Riggs et al. 2014; Shen et al. 2010). The identification of underlying genetic etiology can be used to guide counseling about recurrence risk in the family, aid in establishing prognosis, tailor the care of affected individuals, shorten the 'diagnostic odyssey,' and facilitate access to appropriate early interventions (Dawson et al. 2010; Eriksson et al. 2013; Hayward et al. 2009; Heil and Schaaf 2013; Lintas and Persico 2009; Narcisa et al. 2012; Reiff and Mulchandani 2015; Shen et al. 2010, 2014; Warren et al. 2011).

Since CNVs are more common in individuals with ASD than in controls and may also be associated with other neurodevelopmental disorders (Carter and Scherer 2013), clinical guidelines include recommendations on the use of chromosomal microarray analysis (CMA) for all children with ASD (Manning and Hudgins 2010; Miller et al. 2010; Shen et al. 2010). CMA is a DNA based test that investigates the entire genome in a single analysis, and identifies alterations in the copies of various genomic regions, known as copy number variations (CNVs). CMA identifies genetic changes, including deletions or duplications of genetic material that are not detectable by regular chromosome analysis. CMA analysis, however, does not identify balanced chromosomal rearrangements, single nucleotide changes associated with many genetic conditions, or copy number alterations smaller than the resolution of those detected by the technology in use (Battaglia et al. 2013; Mefford et al. 2012; Roberts et al. 2014).

Results of CMA testing fall into three broad categories: (1) *pathogenic*, a clearly abnormal pattern indicating the presence of a deletion or duplication in a region of the genome that is known to cause pathology (approximately 11 % of cases tested overall); (2) *negative*, a normal pattern, with no potentially pathogenic variants and no etiological diagnosis (80 % of cases); and (3) *variant of unknown significance* (VUS; approximately 9 % of cases), the clinical significance is unknown based on available data or there are incomplete data on the genes in the region (Miller et al. 2010; Redon et al. 2006; Reiff and Mulchandani 2015).

When a VUS is identified in the child, testing for the variant in the parents is offered in order to identify an inheritance pattern. If one of the parents carries the variant and is phenotypically normal, the variant is more likely to be benign. However, the possibility exists that a parent carrying the variant has some minor anomaly or health problem that may be associated with the variant. When the variant appears to be either inherited from a similarly affected parent or is de novo (i.e., neither parent carries the variant), the variant is

more likely to be associated with the phenotype. A similar pattern of inheritance needs to be observed in multiple families before assigning the status of benign or causative to a variant. Additionally, many variants have variable expressivity, which clouds the significance of findings in children whose normal parents also carry these variants (Mefford et al. 2012; Reiff and Mulchandani 2015). There is, therefore, potential for considerable uncertainty in the interpretation of results, and in the implications of results for the children tested and for their parents (Ali-Khan et al. 2009; Battaglia et al. 2013; Darilek et al. 2008; Miller et al. 2010; Redon et al. 2006; Reiff et al. 2012; 2013; Reiff and Mulchandani 2015; Shen et al. 2010; Tabor and Cho 2007).

Investigators have reported that parents were motivated to have genetic testing for children with ASD and developmental delay primarily for early identification, explanation of etiology, and to guide decisions on treatment and reproductive options (Lenhard et al. 2005; Miller et al. 2010; Narcisa et al. 2012; Regier et al. 2009; Shen et al. 2010, 2014; Trottier et al. 2013). However, concerns have been raised about potential harms of genomic information for parents of children with ASD (Rossi et al. 2013; Scherer and Dawson 2011). Scholars have recommended studies of consumer perspectives of the utility of genomic information in order to identify important health and non-health outcomes of genomic testing (Bradbury et al. 2014; Burke et al. 2010; Foster et al. 2009; Grosse and Khoury 2006; Khoury et al. 2010; Scherer and Dawson 2011). Trottier et al. (2013) have reported that participants in genetic research on ASD value receiving genetic testing results because they can alleviate guilt, promote awareness, and may be used to tailor interventions and for family planning. While studies have been conducted on motivations for testing (Chen et al. 2013), experiences with ASD genetic research (Trottier et al. 2013), utilization of genetic testing (Cuccaro et al. 2014), and hypothetical scenarios (Turbitt et al. 2014), this study is the first to our knowledge to explore how parents use information from actual clinical genomic testing of children with ASD.

Materials and Methods

Using a mixed-methods retrospective approach, we examined parents' experiences with genomic testing of children diagnosed with ASD, and their perspective of the usefulness of test results.

The study was conducted between October 2012 and September 2013.

Sample and Recruitment

Participants were recruited from two sources: a cytogenomics laboratory based at an east-coast pediatric teaching hospital, and a commercial genetic testing facility in a western state. Laboratory staff at the two sites identified children with an ICD-9 code of 299.0 ("autistic disorder"), who had undergone CMA testing. Using purposive sampling (Bernard 2013), invitations were sent to approximately equal numbers of participants receiving each of the three types of possible CMA results: (1) pathogenic (a genomic alteration known to cause pathology), (2) variant of unknown significance (VUS) (a deletion or duplication not previously described or not seen in controls) and (3) negative (no clinically significant alteration). Parents were eligible if they were older than 18 years, English-speaking, and had

one or more children diagnosed with ASD and remembered their child having had the CMA test. We invited one parent per family to participate in a telephone interview and online survey and an incentive of $25 was offered. The study was approved by the Institutional Review Boards of the clinical sources.

Our goal was to include approximately 20 participants per result type. Purposive sampling was required because approximately 80 % of tested children receive negative results. Invitation letters and brochures explaining the study were sent to 232 families (143 from the hospital laboratory and 89 from the commercial laboratory), and follow-up phone calls were made until we enrolled 20 participants per result category. We cannot ascertain how many addresses were incorrect, however out of 187 families who were called, 88 (47 %) were not reached (77 did not answer the phone, and 19 were incorrect numbers). Of the 99 who were contacted, 18 (18 %) declined to participate, 13 (13 %) were ineligible, and 68 (68 %) were eligible and consented to participate. Of those who were eligible and consented, 57 parents participated in the study and 11 were not available for an interview after 5 failed attempts to reach them by phone.

Data Collection

Data were collected using online (or mailed paper) self-report questionnaires, and in-depth telephone interviews. A brief initial telephone interview was conducted to confirm eligibility, Participants were reminded about the test and asked whether they recalled receiving the results, and were asked to provide information regarding the child's ASD diagnosis. If they were considered eligible, informed consent was obtained, and information on socio-demographic characteristics (e.g., age, education, race, ethnicity, and number of children) and test result type (pathogenic, VUS or negative) were collected, and a telephone interview was scheduled.

Telephone interviews were conducted by the lead author (Reiff), co-author (Giarelli), and a trained research assistant, using a semi-structured guide. Questions were asked about the impact of test results and how they have been used, advice given by providers about using test results, and what other parents should know about CMA testing. Interviews lasted 30–60 min and were audio-recorded.

Following the interview, the participant was sent the self-report questionnaire. Participants could choose an online or paper format. If online was selected, a link was sent via email. Paper surveys with self-addressed envelopes were sent by regular mail to participants who did not have internet access. The online survey data were collected using Survey Monkey™, and took approximately 15 min to complete. This paper focuses on responses to two items designed by the authors to assess parents' perceptions of the benefits of CMA results: "How helpful has the array test result been for your child?"; and "How helpful has the array test result been for your family?" which were measured using a 4-point scale from "not at all helpful" to "very helpful."

Data Analysis

Survey responses were analyzed using SPSS software and compared across the three result categories (i.e., pathogenic, VUS and negative) using frequencies, means, and non-parametric tests of significance (Mann–Whitney and Kruskal–Wallace).

Qualitative interviews were transcribed, de-identified and entered into NVivo10 (Bazeley 2007), a qualitative software for coding and analysis. Analysis was conducted by assigning codes to sections of the transcripts, categorizing codes into conceptual categories, examining coded data for patterns across respondents and grouping these into themes (Bernard 2013). Initial coding of 4 transcripts was conducted by four of the authors, and a coding scheme was developed collaboratively. Transcripts were then independently coded by two coders, coding inconsistencies were resolved through discussion, and the coding scheme was refined in an iterative procedure. Summaries were formulated for each theme, and the themes were further refined. Frequencies for each code were calculated using matrices (Bernard 2013; Miles and Huberman 1994), in order to explore similarities and differences among participants in different result categories (pathogenic, VUS, negative).

Results

Participant Characteristics

Fifty-seven parents participated in telephone interviews (43 from the hospital and 14 from the genetic testing facility). 84 % of participants were female, 82 % were White 79 % had some college or higher educational level, and the mean age was 42 years (SD 8.7). Of these, 50 parents also completed the survey. The participants who did not complete the survey did not differ significantly from those who did regarding test result type, time since testing and all demographic characteristics. Participant characteristics of the total sample are reported in Table 1.

Survey Results

In the survey, 60.8 % of parents (n = 30) reported that the test result had been moderately, very or extremely helpful both for the tested child and for the family (Table 2). Only parents receiving pathogenic results reported that results were “extremely” helpful. The means of perceived benefit for child and family were not significantly different (at the 0.05 level) across the result categories (VUS, pathogenic, negative), or according to demographic factors (race/ethnicity, education, child age, and recruitment site).

Interview Results

The qualitative analyses revealed five major themes concerning the perceived usefulness of CMA: causal explanation, educational and behavioral interventions, medical care, information for family members, and advancing knowledge. Limits to utility and negative outcomes were also identified. Illustrative statements for the themes and frequencies for each test result category (pathogenic, variant of unknown significance and negative) are presented in Table 3.

Causal Explanation—For many with abnormal and some with VUS results, the test results provided an etiological explanation, and parents felt comforted by finally having an explanation for their child's problems. Several parents reported that the discovery of a genetic variant alleviated their feelings of guilt that they may have done something to cause their child's condition

Several participants discussed the value of having a name or label associated with a genetic disorder. Some parents noted that having a name provided a more tangible identification of their child's disorder. Some reported using the information to explain the child's behavior to others, such as medical providers, teachers, caretakers, and relatives. The test result was used as evidence when trying to have the child's problem acknowledged or to obtain needed services, and was provided as proof to those who previously doubted a medical condition. Specifically, test results helped parents to explain to others that their child's behavior was the result of a medical condition, and not within the child's control, for example, one parent used the result to confront a teacher who "wouldn't work with him, because she said, this kid, there's nothing wrong with him, he just is arrogant, or he just refuses to participate." Confirmation of a medical condition by test results validated parents' personal knowledge and intuitions that there was "something wrong."

Educational and Behavioral Interventions—Many services such as physical, occupational, and speech therapy were already in place for children due to their prior ASD diagnosis, however both pathogenic and VUS CMA results were used by some parents to access additional services through the school district, such as a personal aid in the classroom.

Parents reported sharing the results with teachers and therapists to shape the educational and therapeutic approach (Table 3, B.2). One parent reported that learning that children with the same genetic variation as her child were able to learn to read informed the educational goals for her child. Another respondent stated: "We know what to focus on and we know what [child] will be capable of doing and what we have to do in order to make it work."

Participants reported that the test results helped them to contextualize the child's problems, and enabled them to improve their understanding of the child's behaviors, capabilities, and potential. Several parents, including those with VUS results, reported that the results contributed to their view of the child's condition as more 'concrete' and 'permanent' due to the genetic finding. For many, this new understanding led to increased acceptance, and led some parents to adjust the ways in which they interacted with their child, for example by being less rigid with discipline, for example: "We know why he actually is like he is to an extent, and I know it's beyond his control. It's not something that he can help …I think that, that makes me feel somewhat better".

Some parents reported gaining a better understanding of their child's strengths and weaknesses, and developing more realistic expectations for the child, which enabled them to appreciate small increments of progress and to better calibrate interventions. For example, one parent mentioned that the results helped her to understand her child's very short attention span and how best to work on extending it. Another parent explained that the

family would make efforts, like learning sign language, to better accommodate the limitations of the tested child.

Medical Care for Child—Some parents (n = 13) reported that the genetic results informed medical care for their child. While most had pathogenic or VUS results, two parents commented that they believed that a normal result helped rule out potential genetic conditions. Several participants reported that pathogenic or VUS test results also helped to rule out other suspected genetic disorders such as 22q11.2 deletion syndrome (DiGeorge syndrome), Smith Magenis syndrome or 16p11.2 deletion syndrome. A participant who received a VUS result pointed out that although uncertainty remained about the cause of the child's problems, such a result was preferable to discovering a serious genetic disorder.

In some cases, a genetic variant associated with ASD was also associated with other medical problems, possibly due to a syndromic genetic condition. For example, one parent discovered that individuals with the same genetic variation as her child reacted badly to certain anesthetics, and informed the child's doctors. Another parent stated that "a huge piece of doing the genetic testing" was the discovery of kidney problems, and the need to let caretakers know that her (nonverbal) child can overheat since the child "can't really ask for drinks." Some parents reported that healthcare providers (HCPs) initiated preventive screening for potential serious medical conditions that were associated with a detected variant, such as cancer, heart disease and muscular dystrophy, and referred to medical specialists.

One parent expressed a desire to have had the information earlier to help in treatment planning: "I never would have considered doing half the stuff to poor [child] that we did…" (Table 3, C.4). Three participants expressed hope that detecting genetic causes for ASD in general might influence other parents to abandon approaches that could be futile or harmful, such as avoiding vaccinations and restrictive diets.

Information for Parents and Other Family Members—All three result types (pathogenic, VUS and normal) provided some information relevant to parents and the family. Several parents reported an increased understanding of risk for having another child with ASD. One parent with a normal result explained that it was "a huge factor in our decision to try for another child" (Table 3, D.1.). Others reported that they had already decided not to have more children, explaining that the result validated this previously made decision. One parent stated that if she had known there was a high risk of having a child with special needs, "I don't think we would have had a child… We probably would have done the adoption route."

The test results sometimes affected reproductive decisions only indirectly or not at all. Several participants reported that they needed more information to influence a reproductive decision, either because the result was VUS, or because they (the parents) had not been tested. Several participants discussed the test result playing a potential role in future reproductive decisions of their children or other family members, for example some parents underwent testing themselves in order to learn about reproductive risks for the tested child's

siblings. One participant explained that because of her religious beliefs, the decision to have more children was not affected by genetic risk information.

For some parents, a pathogenic result led them to connect with other families with the same genetic variant, or with organizations (such as rarechromo.org), in the hope of accessing information and support from others facing similar issues. However, several parents with VUS or novel pathogenic results reported that they were not successful in finding and connecting with other families with the same genetic findings.

One participant explained that a pathogenic result helped to inform the family's financial planning. Understanding that the child was likely to remain dependent led the family to create a special needs trust fund.

Several participants articulated that the potential to detect ASD early in a younger sibling was one reason why some parents might consider testing a child already diagnosed with ASD. However, parents in our sample did not report using the results for this purpose themselves. They explained that younger siblings had either already been diagnosed or were clearly not affected, i.e., they had not displayed any features of ASD and were already past the age where these might develop.

Advancing Knowledge, Participating in Research, and Benefit to Others— Several participants, including those with each of the result types, mentioned potential benefits for research and medical practitioners. For several families, a pathogenic or VUS result deemed them eligible to participate in research investigating the genetic variant detected in their child. Participation in research was viewed as an avenue for hope for a potential treatment or pharmaceutical development in the future both for their own child and for others. Many participants felt that by having the child tested, they were contributing to scientific knowledge, which they hoped would eventually lead to benefits for their own child and for other families. Some thought that advancing genetic knowledge about ASD could lead to drug therapies, while others focused on the diagnostic benefits.

Limits to Utility and Negative Impact—Limits to utility were expressed by approximately half of the participants and are presented in Table 4. Many participants with pathogenic (N = 9), as well as those with VUS (N = 12) and negative (N = 11) findings, reported that the test did not lead to any specific changes for the child tested or the family regarding the approach to medical care or therapeutic interventions. Reasons included the lack of any new treatment options that could ameliorate the child's condition, and no change to the family's day-to-day experience. Many also noted that services and interventions were already being received based on the child's ASD diagnosis, and were not affected by test results. Some expressed that the results merely confirmed what they already knew to be true about their child, for example: "He's a person, and his personality tells me more about him than his test does."

Most participants who reported limits to utility also expressed that it was nevertheless advantageous to be more informed, and that the test results had educational value for families, healthcare professionals and teachers. Some participants explained that positive

test results were beneficial for their child's doctors, in terms of gaining a better understanding of the child's condition and a sense of satisfaction in resolving a puzzling diagnostic question.

Some parents identified psychosocial harms from learning positive CMA results. For example, one participant reported that her relatives blamed her husband for the child's condition when it was discovered that he carried the same genetic variant as their child. In contrast to those who felt that a genetic finding alleviated their feelings of guilt, another parent expressed that the genetic explanation actually contributed to her sense of guilt: "I fear that something about me made him come out wrong."

Some parents experienced confusion or misunderstood the genetic information. In some cases, participants' perceptions of risk were inconsistent with scientific explanations, for example, in a family where the older son had a pathogenic variant and the second son did not, the participant expressed a scientifically inaccurate view that the genetic variant would affect "every other boy."

Some parents who received negative results expressed the view that "there's not a genetic connection," indicating a potential misunderstanding of the result and failure to recognize that there may still be an undetected genetic abnormality, even with a negative CMA.

Discussion

This study explored parents' perspectives of the utility and the potential positive and negative value of clinical genomic testing of children with ASD. In the survey, the majority of parents reported that the test result had been helpful for their child and family. In the qualitative data, over half the sample, including many with pathogenic results, reported that the results did not lead to specific uses related to medical care, and limits to utility were expressed when the test did not lead to changes in medical care or therapeutic interventions. These data revealed the importance of non-medical uses of test results for families, such as access to services, reproductive decision-making, explaining etiology, and simply providing additional information.

Our finding in the qualitative data that parents reported some positive value to having genomic results even in the absence of effective medical treatments is consistent with prior research on genetic testing for susceptibility to Alzheimer disease (Chao et al. 2008). Many parents who did not report specific medical uses for test results did express a benefit of feeling more informed, even if the information did not have direct relevance to medical care. Additionally, the genetic information had utility beyond the child tested, including benefits for other family members. Our findings demonstrated varied ways in which families use genomic information, and support a conceptualization of utility that includes medical and non-medical dimensions (Bradbury et al. 2014; Burke et al. 2010; Foster et al. 2009; Grosse and Khoury 2006).

Research on the clinical utility of CMA has shown that benefits of identifying genetic causation include improved anticipatory guidance, medical management, identification of children at risk, accuracy of recurrence risk estimates for future pregnancies, access to

individualized, tailored services, and a reduction in the cost and stress of lengthy diagnostic workups (Henderson et al. 2014; Narcisa et al. 2012; Shen et al. 2010). Our findings suggest that CMA results can be useful not only in initiating preventive screening, but also in helping to avoid interventions that may be futile, thereby saving time and financial resources.

Previous research found that parents expressed interest in using genetic testing to assess the risk of ASD in younger siblings of affected children (Chen et al. 2013; Narcisa et al. 2012), and this is frequently reported as a major potential value of genomic testing for ASD (Schaefer and Mendelsohn 2013; Shen et al. 2010, 2014). Parents in our study did not report using results for this purpose, explaining that younger siblings were either already diagnosed with ASD or were not displaying potential symptoms. However, participants did suggest that the test might be used for this purpose by other parents in the future. Additionally, while some parents used results to inform reproductive decisions, most parents had already made decisions prior to testing. Future research should investigate the use of clinical CMA results to identify ASD and initiate early interventions among younger siblings of children tested, and to guide reproductive decisions.

For some parents in our study, a genetic finding helped to accept the diagnosis and alleviate self-blame and feelings of responsibility for having somehow caused the problem during pregnancy or early infancy. These findings were consistent with prior research showing that an etiological diagnosis can be useful in providing relief from guilt and a sense of acceptance (Lenhard et al. 2005; Lipinski et al. 2006; Makela et al. 2009). However, some parents reported that the genetic information contributed to a heightened sense of guilt and self-blame, for unknowingly passing on a potentially pathogenic genetic variant. It has also been noted that genetic etiology can lead parents, teachers and health care providers to lower their expectations for improvement or recovery (Dar-Nimrod and Heine 2011; Lebowitz et al. 2013; Walsh et al. 2011). This issue is extremely important for families with ASD, with its broad range of severity and symptoms, and treatment options that involve primarily behavioral interventions. Counseling should be provided to enable parents to have realistic goals without setting limits on the child's potential.

The use of the result as concrete evidence of a medical condition, and as "ammunition" in what is often a struggle to have the child's problem acknowledged or to obtain resources is consistent with previous studies reporting that genetic results can be validating and empowering for parents (Reiff et al. 2012; Trottier et al. 2013). Despite already having a diagnosis of autism, genetic results may help some families to access additional services, such as a personal aid in the classroom, or to more specifically guide the therapeutic and educational approaches that were already in place. They can also help in explaining the child's behavior to others, including teachers and family members.

Parents in our study identified potential value of testing in general that was distinct from the utility of their own specific test results, including future benefits for other families and for medical advancement. Studies with parents of children with ASD have reported that contributing to genetic research can be a powerful motivator for testing (Chen et al. 2013; Miller et al. 2010; Trottier et al. 2013), and can provide a sense of control and hope (Trottier

et al. 2013). Although the testing in our study was for clinical purposes, and not research, many parents felt that they were contributing to medical knowledge by having testing, which could potentially benefit others in the future, or even lead to tailored treatments for their own child. Our study suggests that healthcare providers can support families by identifying results that may have potential future utility, offering guidance for appropriate follow-up, and acknowledging the role of families in contributing to medical advancement, even when testing is for clinical, and not for research, purposes.

In the qualitative data, a few parents expressed that testing had a negative psychosocial impact, for example feelings of guilt or blame in response to the knowledge that they or their spouse has passed on a genetic condition to their child. Additionally, for parents of children with ASD, the discovery of a genetic variant may be accompanied by the realization that one of the parents has features consistent with ASD or broad autism phenotype (BAP) (Sasson et al. 2013), that were previously unrecognized as such. Testing has some known risks and limitations including the fact that a negative result does not exclude a genetic etiology; incidental findings unrelated to the reason for testing may be found; and results of uncertain significance may be associated with prolonged uncertainty for the family (Burke et al. 2010; Fanos 2012; McMahon et al. 2006; Scherer and Dawson 2011; Yudell et al. 2013). The potential repercussions of genomic testing for ASD should be considered and discussed in pre- and post-test counseling.

Our findings also highlight the challenges for parents in making use of CMA results when their implications may be uncertain. Survey results were interesting in that the perceived benefit of CMA did not differ significantly by result category (pathogenic, VUS and negative). This may be due to the continuing uncertainties regarding prognosis inherent in each of the result categories. Many pathogenic findings involve rare and newly identified genomic disorders for which prognostic information may not be available (Cooper et al. 2011). Turbitt and colleagues reported that some parents may use knowledge of a VUS detected in their child to guide decision making in future pregnancies (Turbitt et al. 2014). While VUS is by definition uncertain, some parents perceive a VUS result as useful simply because it identifies a genomic variation, with the potential to provide more information in the future, or an opportunity to participate in research. A reporting scheme is now used in some laboratories that differentiates between VUS results that are “VUS,” “VUS—likely pathogenic” and “VUS—likely benign” (Green et al. 2013; Kearney et al. 2011; Schaefer and Mendelsohn 2013). Future studies are needed to assess the impact of the categorization of uncertain CMA results on interpretation, understanding and utility, and to ascertain the clinical and personal value of novel pathogenic findings.

A disturbing finding of our study was that several parents with negative results believed that a genetic causation had been ruled out, apparently not understanding that many genetic mutations and variations are not detectable by CMA. This suggests that negative results should not be delivered in a perfunctory way. There is a need for post-test counseling for families receiving negative, as well as pathogenic and uncertain results. Some parents also expressed that they would have liked more explanation about the CMA results and guidance about how to use them. Research has shown that lay understandings of genetics are limited (Condit 2010; Haga et al. 2013), that poor understanding of the benefits, risks, and

limitations of testing can interfere with informed decision making (Selkirk et al. 2009), and that genetic counseling can improve understanding and coping (Biesecker and Erby 2008; Lipinski et al. 2006). It is important to recognize that misunderstandings can impede appropriate use of results by patients and families, and that a referral to a genetic counselor may be helpful.

In our sample, the CMA tests were ordered primarily by non-genetic clinicians (developmental pediatricians, neurologists, and pediatricians). Genetics expertise is likely to affect the quality of counseling provided about CMA test results (Kegley 2003; Reiff et al. 2012, 2013; Rosas-Blum et al. 2007). Future studies should investigate the differential impact on understanding and outcomes of testing based on the genetic expertise of clinicians ordering the tests and providing results. Improved counseling could potentially improve the way patients and families make use of their results.

It has been recommended that healthcare providers tailor genomic counseling sessions to patients' informational needs (Bradbury et al. 2014). One way they might achieve this is by considering parents' perspectives regarding use of test results, and drawing on this information as a framework for discussing the ambiguities inherent in the genomic information derived from CMA, as well as in the nature of the autism spectrum diagnosis. Discussion of the ways in which CMA results can be used in health and non-health contexts may help healthcare providers and parents to make more informed testing decisions and better use of test results. It has been suggested that randomized clinical trials are needed to assess the clinical utility of genomic testing for autism (Agency for Healthcare Research and Quality (AHRQ) 2014). If such trials occur, parental perspectives on what constitutes utility should be considered, since the subtleties and nuances of parental perspectives may differ from clinicians' perspectives of utility.

Limitations

Generalizability is constrained by the study sample, which is limited in size and diversity. Therefore, we could not investigate the ways in which perceived utility may differ by socio-demographic characteristics, age of the child when tested, and in cultural context. This study is strengthened, however, by recruitment from two testing sites in different geographic locations, and by inclusion of participants receiving negative, as well as uncertain and pathogenic results. The purposive sample provided three groups of comparable size in order to assess utility across different result types, but the study was limited by a fairly low response rate. It is possible that there was some bias in the sample, for example if parents of children with more severe illness, or those who had poorer understanding or less interest in the test were less likely to participate. It is also possible that parents' perspectives regarding their CMA results varied according to the severity of their child's condition, or concurrent medical conditions. Additionally, this retrospective study did not assess pre-test parental perceptions. A future prospective study could explore the impact of pre-test perceptions and counseling on outcomes of testing.

Conclusions

This study reported parental perspectives on the actual use of CMA results, including health and non-health dimensions (including explaining the child's behavior to others, and alleviating feelings of guilt) that would be important for families and healthcare providers of children with ASD to consider when making decisions about testing and when receiving results. Adequate genetic counseling and follow-up are needed for families with all result categories (pathogenic, VUS, and negative) in order to maximize the clinical and personal utility of the test. This can help to prepare for and address potential disappointment when testing does not lead to new treatment options or other tangible changes for the child. Healthcare professionals can play a role by considering parental perspectives, clarifying the limitations of the test in advance, and discussing potential medical and non-medical uses of the information. By providing insight into parents' perspectives on the value of CMA testing, this study can contribute to the debate surrounding the relevance of both health and non-health related utility in genomic testing.

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Table 1

Participant characteristics (N = 57)

Demographic information	N	Percentage (%)
Parent age		
25–29 (years)	3	5
30–39	23	40
40–49	18	32
50+	10	18
Unreported	3	5
Parent race		
African American	6	11
White	47	82
Asian	1	2
Mixed	3	5
Parent education		
Less than high school	4	7
Completed high school	8	14
Some college	14	25
Graduated college	16	28
Post graduate	15	26
Parent gender		
Male	9	16
Female	48	84
Child gender		
Female	11	19
Male	46	81
Child age (at interview)		
0–3 (years)	4	7
4–6	19	33
7–9	13	23
10–14	12	21
>15	9	16
Time since test		
5–12 months	27	47
13–18 months	8	14
19–24 months	4	7
25+ months	15	26
Unreported	3	5
Source of recruitment		
Hospital	43	75
Genetic testing facility	14	25
Ordering provider		

Demographic information	N	Percentage (%)
Developmental pediatrician	15	26
Neurologist	10	18
Pediatrician	7	12
Geneticist	7	12
Metabolic/endocrinologist	2	4
Other (1 psychiatrist, 1 speech doctor, 1 pulmonologist, 1 nurse practitioner)	4	7
Unknown	12	21

Table 2

Survey responses indicating perceived overall benefit for the child and family by result category (N = 50)

Result type	Not at all helpful % (n)	Not very helpful % (n)	Moderately helpful % (n)	Very helpful % (n)	Extremely helpful % (n)	Mean (SD)
How helpful has the array test been for your child?						
Pathogenic (N = 15)	20 % (n = 3)	20 % (n = 3)	33 % (n = 5)	13 % (n = 2)	13 % (n = 2)	2.80 (1.32)
VUS (N = 17)	29 % (n = 5)	18 % (n = 3)	41 % (n = 7)	12 % (n = 2)	0	2.35 (1.06)
Negative (N = 18)	6 % (n = 1)	28 % (n = 5)	39 % (n = 7)	28 % (n = 5)	0	2.89 (0.90)
Total (N = 50)	18 % (n = 9)	22 % (n = 11)	38 % (n = 19)	18 % (n = 9)	4 % (n = 2)	2.68 (1.10)
How helpful has the array test been for your family?						
Pathogenic (N = 15)	20 % (n = 3)	13 % (n = 2)	27 % (n = 4)	20 % (n = 3)	20 % (n = 3)	3.07 (1.44)
VUS (N = 17)	24 % (n = 4)	29 % (n = 5)	29 % (n = 5)	18 % (n = 3)	0	2.41 (1.06)
Negative (N = 18)	0	33 % (n = 6)	39 % (n = 7)	28 % (n = 5)	0	2.94 (0.80)
Total (N = 50)	14 % (n = 7)	26 % (n = 13)	32 % (n = 16)	22 % (n = 11)	6 % (n = 3)	2.80 (1.12)

Table 3

Perceived uses of CMA results: themes and illustrative statements

Theme [frequency by P, V, N result type][a]	Statement
A. Causal explanation	
1. Provided an explanation [10-P; 7-V; 0-N]	I think a lot of parents of autistic kids have an immense amount of guilt about how this could have happened… what did I do that caused my child to have this condition? And I think it did kind of alleviate that. …This is a situation where there was just bad coding when the egg and the sperm met. It was just one of those things that happens. It was nothing that we did before or after that would have changed this result. And so, I think it helped a little bit for that. [P#06][b]
2. Having a diagnosis; evidence of a medical condition [5-P; 2-V; 0-N]	To actually see it in writing—it validated that I'm not a crazy woman either. It's one thing for mommy to say it, but it's another thing to have it validated. [P#18] I had to get proof in the pudding, which basically is one of the reasons we took the genetic stuff. To say, look, … 'look, see. It's right here, black and white.'…It gives you more of a sure thing, a more black and white thing that you can show people that's wrong with your kid. Even though it is unknown, I can say, 'hey, yes there is something wrong with him, here's the genetic problem that caused this. '[V#17]
B. Educational and behavioral interventions	
1. Access to services [5-P; 2-V; 0-N]	Well, he was already receiving a lot of the basics like speech, PT, OT, he's also in an all-day autistic support class. [The test result] helped get him a one-on-one aid, who is there in the school with him and she's there just for him, just to help him. [P#25]
2. Inform educational and therapeutic approach [7-P; 4-V; 0-N]	We were struggling …what do we do? Do we teach him how to clear the dishes from our table, or do we teach him how to read and write? …. I think it has informed our IEP [Individualized Educational Program] goals….I can say, 'his geneticist says that kids like [child] are good readers; that they have these difficulties, and these are good strategies to work with him.' [P#06]
3. Improve understanding and acceptance [8-P; 4-V; 0-N]	So now I'm actually able to accept the fact that his timeline may be a little bit different,…it's more of trying to figure out what are his strengths so that I can steer him more into those areas. [V#12] I was able to realize that this is a permanent part of his genetic makeup and something that we'll be dealing with over the long term, instead of trying to find a quick solution. …I think even though we don't know what those mean, the fact that those genetic markers are incomplete tells us, you know, there's just something about the way he's put together that's just a little different, and—at least right now—we can't rebuild those markers, so this is—it is what it is. [V#29]
C. Medical care for child	
1. Rule out potential serious genetic disorders [2-P; 1-V; 2-N]	My child was tested because at the time, both my kids were diagnosed with autism and one of the things that we needed to do was rule out Fragile X. [V#53]
2. Inform medical treatment [9-P; 4-V; 0-N]	I have put her on anxiety medication … because I know these kids [with this genetic variation] definitely have a lot of anxiety. So it might not have caused me to go on the medication, but it was another factor in deciding to go ahead and do it. [P#09] I basically have to share this with the school nurse or the staff members that [child] can overheat. She doesn't sweat that much and it has to be in a record. Otherwise somebody who's caring for her really could misinterpret a lot [P#18]
3. Preventive screening and monitoring [5-P; 2-V; 0-N]	It has had me seek additional tests, medical testing for [child]. This particular population has had some sudden unexplained deaths of children that looked otherwise healthy. And so, we did an EEG, and so we did a heart thing, we did a seizure screening and blood tests for different other things that he could have had. So we had baseline medical testing done for him, because he might have had a heart condition and we wouldn't have known. [P#06]
4. Avoid futile interventions [2-P; 1-V; 0-N]	If I had had this diagnosis [15 years ago], I never would have considered doing half the stuff to poor [child] that we did. … here I am paying people $1000 a visit [for chelation]. … You're thinking you're doing the very best by your kid in doing these things. … I never would have done those things to [child] if we had this diagnosis. [P#18]
D. Information for parents and other family members	
1. Inform reproductive decisions [0-P; 4-V; 2-N]	It played a huge factor in our decision to try for another child. … Knowing that there was a little less risk … was a huge relief and it was something that we needed to have in our determination to continue our family. … If the genetic counseling hadn't been available to us, we probably wouldn't have taken a shot in the wind. We probably would have just stopped at my son. [N#21]
2. Connect with other families and support groups [3-P; 2-V; 0-N]	[The doctors gave] no guidance or direction… I feel like I get more information when I Google, and I'm on several different Facebook sites … and that's where I get a lot of information. [P#15][b] Someone at [Lab] has actually given us the name of one parent who allowed—to talk. I haven't connected with her just yet, but I think it's huge in knowing what other kids similar to [child]'s age, where they're at and are they in a group home setting. Are they able to hold a job? Are there differences? [P#18]

Theme [frequency by P, V, N result type][a]	Statement
	I never would have heard of the Unique group before that, or even the NIH. I didn't know that they had—you would think I would have thought that, but I didn't know they had a whole section on genetics and rare disorders. [P#19]
3. Financial planning [1-P; 0-V; 0-N]	We had a trust fund set up from a family member for my kids. We got that fixed … into a special needs trust. So that if anything happens to [me, or to my husband, that money is there for somebody to help take care of him. [P#02]
4. Feel more informed [9-P; 3-V; 1-N]	How do I use it? I'm just more informed. Use it? I wouldn't say I—I just am more informed about what's going on with my child. [V#67]
E. Advancing knowledge, participation in research, benefit to others	
1. Participate in research studies [1-P; 3-V; 1-N]	I know it's maybe a pipedream, but we all hope as parents with children like [Child] that there's some sort of drug therapy or something that would maybe bypass whatever's happening genetically to maybe give him help. [V#33] We could be part of a study. …. I think that it gives us a ray of hope that there could be some kind of help for our son in the future, you know, in terms of pharmaceuticals. [P#06]
2. Benefits doctors [4-P; 1-V; 1-N]	I think they [doctors] were fascinated to find that out because they … didn't know what was wrong. And so to actually have something concrete where they could read about the kids with the same thing, I think it was helpful for them just education-wise. [P#15]
3. Contribution to scientific knowledge [2-P; 4-V; 0-N]	I think if we don't, as a society, look at these things, don't try to move forward with our research and understand these things better, then we won't get anywhere as far as drugs and treatment for diseases. So even though [Child] may not benefit directly at this point, or he may, you know, years down the road, we have to increase our understanding as a society of how all these little defects kind of come into play in relation to autism.[V#11]

[a] P, pathogenic CMA result; V, variant of unknown significance CMA result; N, negative CMA result

[b] Result type and ID number follow each quote

Table 4

Limits to utility: themes and illustrative statements

Theme [Frequency by P, V, N result type][a]	Statement
No change in approach [9-P; 12-VUS; 11-N]	It doesn't affect him. It does nothing to him. Absolutely nothing. It doesn't make anything worse, better, nothing. It just is there. … I really don't think I had gotten something out of it, really at all, because it didn't bring me closer to making everything go away from [child] I guess you could say [P#20][b] I talked to my service coordinator…, and she said yeah, it's not going to change anything that he's going to get, or he's not going to get in the future. [P#23]
Negative value [P-2; VUS-2; N-0]	I feel a lot of guilt that I carried him inside of me and his physical genetic makeup is not correct, so I think I carry a lot of guilt that somehow I did that. Somehow I contributed to—even though logically I know I probably didn't. I just fear that something about me made him come out wrong. [P#15] They [my parents] didn't like my husband in the first place. … So they were expecting it to be from him anyway. It just didn't make my husband feel very good. I was kind of wishing it was from me instead. [V#17]
Misunderstandings and ambiguities [P-3; VUS-4; N-1]	I tried to find it on the internet as to what it would mean, but I couldn't understand a damn word of it. [P#20] I'm thinking, well wait a minute, what just happened, I thought, you know, I thought this is what he had and then it isn't what he had and—so there is a bit of confusion. [V#24] This isn't a reason for it. Like there's not a genetic connection. [N#49]

[a] P, pathogenic CMA result; V, variant of unknown significance CMA result; N, negative CMA result

[b] Result type and ID number follow each quote