HHS Public Access

Author manuscript

*J Genet Couns*. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

*J Genet Couns*. 2016 October ; 25(5): 1116–1126. doi:10.1007/s10897-016-9943-z.

# "Something extra on chromosome 5": Parents' understanding of positive prenatal chromosomal microarray analysis (CMA) results

**Sarah A. Walser**[1], **Allison Werner-Lin**[2], **Amita Russell**[3], **Ronald J. Wapner**[3], and **Barbara A. Bernhardt**[1]

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

[2] School of Social Policy and Practice, University of Pennsylvania, Philadelphia, PA

[3] Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY

## Abstract

This study aims to explore how couples' understanding of the nature and consequences of positive prenatal chromosomal microarray analysis (CMA) results impacts decision-making and concern about pregnancy. We interviewed 28 women and 12 male partners after receiving positive results and analyzed the transcripts to assess their understanding and level of concern about the expected clinical implications of results. Participant descriptions were compared to the original laboratory interpretation. When diagnosed prenatally, couples' understanding of the nature and consequences of copy number variants (CNVs) impacts decision-making and concern. Findings suggest women, but less so partners, generally understand the nature and clinical implications of prenatal CMA results. Couples feel reassured, perhaps sometimes falsely so, when a CNV is inherited from a "normal" parent and experience considerable uncertainty when a CNV is *de novo,* frequently precipitating a search for additional information and guidance. Five factors influenced participants' concern including: the pattern of inheritance, type of possible phenotypic involvement, perceived manageability of outcomes, availability and strength of evidence about outcomes associated with the CNV, and provider messages about continuing the pregnancy. A good understanding of results is vital as couples decide whether or not to continue with their pregnancy and seek additional information to assist in pregnancy decision-making.

### Keywords

microarray analysis; prenatal testing; understanding; copy number variant; genetic counseling

**Corresponding Author:** Sarah Walser, Translational Medicine and Human Genetics, University of Pennsylvania Perelman School of Medicine, 3400 Spruce St., Silverstein 5, Philadelphia, PA 19104, 215-662-4910, Sarah.Walser@uphs.upenn.edu.

Conflict of interest statement

Sarah Walser, Allison Werner-Lin, Amita Russell, Ronald Wapner, and Barbara Bernhardt declare they have no conflict of interest

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

## Introduction

Chromosomal microarray analysis (CMA) detects copy number variants (CNVs), including chromosomal microdeletions and microduplications associated with a variety of cognitive disorders and congenital anomalies, and predisposition to neurodevelopmental conditions including schizophrenia and autism. CMA's increased yield over traditional karyotyping (Crolla et al. 2014; Wapner et al., 2012) led the American College of Obstetrics and Gynecology (ACOG) to recommend prenatal CMA testing be considered a first tier test following detection of an ultrasound anomaly, and made available when performing invasive genetic testing for any indication including maternal age (American College of Obstetricians and Gynecologist 2013). The increased diagnostic yield of CMA is, however, accompanied by the possibility of finding CNVs of uncertain clinical significance (VUS), incomplete penetrance, or variable expressivity (Martin et al. 2015) with a wide range of associated phenotypes ranging from apparently normal to severely affected.

Despite these complexities, prospective parents often want all available information about their pregnancy, (Norton et al. 2014; Turbitt et al. 2015; Walser et al. 2015; Willis et al., 2015; van der Steen et al. 2015) although this may vary depending on culture and values (Alsulaiman et al. 2012; Nahar et al. 2013). When uncertain results are found, information may be poorly understood (Hillman et al. 2015) and parents often experience distress (Bernhardt et al. 2013; Werner-Lin et al. 2015). In such cases, even small changes in risk can shape women's risk perception and pregnancy choices (Richards et al. 2015). Incomplete or incorrect understandings could lead a woman to terminate a pregnancy. Alternatively, parents may feel blind-sided and unprepared following the birth of a child with an unexpected severe phenotype. Providers, too, may not adequately understand CMA results, especially VUS results (Cypowyj et al. 2009; Hanoch et al. 2014; Kiedrowski et al. 2015; Reiff et al. 2015), making it difficult to guide informed patient decision-making. Parents often seek additional information outside the consult room (Reiff et al. 2012; Roche & Skinner 2009), such as online or through support or advocacy groups dedicated to specific conditions. Precise recall of the specific CNV carried by the child is critical so that parents retrieve relevant information, when such information is available.

To our knowledge, only limited research has examined how the understanding and response to prenatal CMA test results impacts decisions about pregnancy termination. We interviewed woman and their partners who received positive CMA results to understand how parents remember, interpret, and respond to their results.

## Methods

Researchers analyzed transcripts of interviews with women and their partners to explore their understanding of, and concern about, receiving positive prenatal CMA results. The study protocol was approved by institutional review boards of the University of Pennsylvania and Columbia University.

## Recruitment of Participants

Researchers recruited pregnant women through antenatal testing centers collaborating with Columbia University on an NIH-funded project "Prenatal Microarray Follow-Up Study." Shortly after receiving microarray results, women received a pamphlet inviting them to complete a short online survey eliciting demographic information, test results, and informational needs (Walser et al. 2015). Women indicating abnormal or uncertain results responded to questions about the variant, intent to continue the pregnancy, and interest in being interviewed. Respondents were contacted to provide additional study information, and to schedule an interview. Of the 152 female survey respondents, 36 had abnormal results or a VUS and 28 of those were willing to participate in an interview. Following the interview, researchers asked women for permission to contact their partners and then emailed partners with interview information. Twelve male partners were willing to participate in an interview.

## Interviews

The research team developed a semi-structured interview guide to elicit feedback about testing experiences and decision making about test results. Women and men were interview separately. Verbal informed consent was obtained from all participants before beginning the interview. Study staff conducted phone interviews between 2 and 15.5 weeks (median of 7 weeks) after participants received CMA results. Interviews were digitally recorded and lasted between 30 and 80 minutes, with a median length of 55 minutes. Participants were compensated with a $25 gift card. Interviews were transcribed, checked for accuracy, de-identified, and uploaded into NVivo10 to facilitate coding and analysis.

## Analysis

We evaluated participants' recall and description of results using three criteria: 1) inherited versus *de novo*; (2) deletion or duplication; and (3) the associated chromosome or syndrome name. The research team, including two genetic counselors, compared each criterion to the official laboratory report and labeled each as 'correct', 'incorrect', or 'missing' (when relevant information was not mentioned by the participant). To assess understanding, we compared participants' descriptions of the CNV and possible phenotypic outcomes with information detailed on the laboratory report, and online databases, such as UNIQUE, ClinVar, Simons VIP, and PubMed.

Two researchers independently conducted focused coding of emotional language about CMA results, fetal development, and pregnancy outcomes to distinguish categories, or levels, of concern. Researchers compared coded data and identified three levels of concern: *significantly, somewhat, or not concerned.* Disagreement about data coded as *somewhat concerned* and *not concerned* was resolved with the addition of a *lingering doubt* classification. During focused coding, researchers identified a list of factors participants articulated as impacting concern about pregnancy outcomes.

## Results

Twenty-eight female patients and 12 of their male partners completed interviews. The majority of participants were well educated (93% with a college degree or higher) and White (86%) (Table 1). Advanced maternal age was the most common indication for testing.

### Overview of findings

Overall, women accurately recalled details about the CNV and described in greater depth than male participants the possible phenotypic involvement associated with their finding (Table 2). Participants varied in the level of concern about pregnancy outcomes; of the 28 women, two were *significantly concerned* about the impact of their finding on the fetus, 11 were *somewhat concerned*, six expressed *lingering doubt*, and nine women were *not concerned*. Of the 12 male partners, one was *significantly concerned*, five were *somewhat concerned*, one had *lingering doubt*, and five were *not concerned* (Table 3).

Five factors in dynamic interaction influenced participants' concern about the impact of their CNV. These included the pattern of inheritance (inherited or *de novo*), type of possible phenotypic involvement, perceived manageability of these outcomes, availability and strength of evidence about outcomes associated with the CNV, and provider messages about the clinical impact of the CNV.

### Recall and description of results

All participants accurately recalled whether the fetus's CNV was *de novo* or inherited (Table 2). Nearly all women accurately recalled the chromosome involved (86%) and whether it was a deletion or duplication (100%). Conversely, fewer men recalled details about their results, including the chromosome involved (67% recalled) or whether it was a deletion or duplication (50%).

Within couples, women's recall of CNV information was superior to their male partners. For example, one woman correctly recalled, "it was a partial deletion...I think it was chromosome 3". Her partner stated, "I'm not sure if it was a chromosome or what the issue was." In the following couple, both partners accurately identified the chromosome involved in their microarray findings. The woman correctly reported, *"a duplication at chromosome 22q spot 11."* Her husband was less sure, reporting "I can't remember which letter or number it was-— it was 22 or something."

Most women accurately reported some phenotypic involvement as described in their lab report, yet most did not describe the complete range reported. One woman described "the range of behaviors from autism to mild to moderated retardation" but did not mention other phenotypic possibilities including motor delays, learning disabilities, and ADHD. Men reported fewer details about possible phenotypes. One husband, overwhelmed by the range and severity of the possibilities, chose to shut them out, saying: "I think my wife mentioned something about psychopath and I tried not to take it all in..."

Reported provider language did not always facilitate participant understanding of CNVs. One woman recalled the terminology used, but not the significance: "...the gene is

spliced...that's where everything gets fuzzy for me because I don't really understand how all that works." Although technical information was difficult for participants to meaningfully interpret, most understood whether variants conferred physical and/or psychiatric risk. Overall, however, fewer participants mentioned risk of severe psychiatric disorders than risk of developmental or other health conditions.

### Information Seeking

To help understand the possible impact of their CMA result, many participants sought information online and a few connected with support groups dedicated to children with similar CNVs. Absent information about the implications of the CNV, participants such as this woman added their own meaning: "Now I'm wondering if his chromosomes mixed with my chromosomes is causing all these issues."

### Concern about CNVs

CMA results triggered varying levels of concern about the impact on the fetus (Table 3). Two of the three women carrying a fetus with a clearly pathogenic CNV expressed *significant concern,* and two ultimately decided to terminate their pregnancy due to the challenges the baby would face if carried to term.

Participants who expressed being *somewhat concerned* were generally those whose fetus carried a *de novo* CNV or two CNVs. These participants anticipated a prolonged period in which they would question their child's development due to the presence of the CNV. One woman shared: "For the first five years of her life, every time she does something that's behind my son or if she walks differently... I'm gonna think 'well is this the deletion?"

Participants with *lingering doubt* expressed guarded confidence that their child would "probably" develop typically and used qualifiers to share that they felt "pretty comfortable" with the decision to continue the pregnancy, as this woman described: "Generally speaking I think we feel okay that we're pretty confident that it will be fine." The use of multiple linguistic qualifiers reflected the lack of clarity about phenotypic outcomes.

Participants who were *not concerned* about their CNV expressed confidence that the findings would not negatively impact the health and development of their child.

### Moderators of Concern

Laboratory reports given to participants included classification of results (benign, likely benign, VUS, likely pathogenic, or pathogenic). These classifications did not appear to impact participants' levels of concern (Table 4) and were infrequently mentioned by participants. The moderators of concern (Table 5) voiced by participants are discussed below.

**Inheritance—**After identifying a CNV in the fetus, testing of biological parents helped to classify the variant as inherited or *de novo.* When the variant was identified in a "normal" parent, concern frequently transformed into confidence, even when it was classified by the

lab as a VUS. One mother stated, “He was quite relieved to hear that it was paternally inherited. He's reasonably healthy ... it would be a total non-event.”

**Type and severity of possible phenotypic involvement—**Participants considered a range of physical, cognitive, and psychiatric impairments associated with the CNV. The two who terminated understood their result indicated a well-known and life-limiting condition. For other participants, ultrasound usually provided some evidence the baby was free of obvious birth defects. These participants centered attention on possible neurocognitive involvement, especially learning disabilities and autism risk. One participant viewed these concerns as a deciding factor in continuing the pregnancy, stating, “Any mental or developmental limitations would be a no-go. And then physical limitations would depend on what they were...”

**Manageability—**Participants imagined parenting a child with the CNV-associated condition, weighed best and worst case scenarios, considered their expectations of parenthood, and evaluated resources available to support the possible needs of their future child. Some participants expressed a heightened sense of control over what they might encounter after birth: “the worst case scenario is if he has a learning disability or he's developmentally delayed, and that's manageable, especially with early intervention.”

Participants varied in the extent they felt prepared for a child with symptoms ranging from neurocognitive impairments to profound physical disabilities: “Part of me would think ‘there are successful autistic people out there’...the other part of me might think like ‘I'm just not ready for this.’” Some participants felt equipped to care for a child with developmental delays, while others did not.

**Strength of evidence—**Participants found comfort when robust evidence provided clarity about their specific CNV. This included medical literature and information from additional screenings, including ultrasounds, which showed no structural abnormalities: “There was actually a lot of literature about being able to diagnose this on MRI and ultrasound, so we felt comfortable that at this late stage we're not seeing anything.” The strength of probabilistic evidence about phenotypic involvement was key information when deciding about pregnancy termination: “Had I been given a higher percentage than [the 10%] I was given, I probably would not have proceeded.” Probabilities permitted focus on concrete information. When no probabilistic information was available, some became frustrated and struggled to grasp the significance of their results: “All I want is a probability. It just would be a lot easier to deal with.”

VUS results posed a unique challenge to participants as they coped with little or no information about the meaning of their findings. Some were relieved to learn there was no evidence suggesting a definite problem. One woman said: “I wasn't too worried because they said that they don't know any clinical significance yet.” Her husband echoed this sentiment saying: “...we were told that it has no known clinical significance... we [were] relieved of any real worry.” For most participants, however, the lack of information about the likelihood and degree to which their fetus might be affected exacerbated concern. One woman stated,

"The part that freaked us out was definitely the spectrum to which they had associated my specific duplication...I don't feel like there was enough information."

**Provider messages—**All participants wanted providers to interpret CMA findings and most consulted with more than one. While providers often spoke about genetic concepts and location of the CNV, participants were most concerned with the implications of the findings. One participant explained that the technical information was irrelevant to her concerns about the CNVs impact on her baby: "I had to ask them what it was... like a triplication of chromosome like blah, blah, blah...or like gene blah, blah, blah on chromosome 8." When providers offered either overt or covert messages regarding the expected phenotype and recommendations to continue or terminate the pregnancy, these messages either fortified participants' concerns or offered them reassurance, as this woman shared: "The genetic counselor put such a great spin on the whole thing that I felt really comfortable and confident about everything that's gonna take place after the birth."

## Discussion

Accurately understanding prenatal CMA results is crucial as parents make decisions about continuing or terminating a pregnancy. Our findings suggest female patients generally understood the nature and phenotypic possibilities associated with CMA test results. Men's understanding and recall were more uncertain or incomplete. All participants knew whether their baby's CNV was inherited or *de novo*, likely reflecting the binary nature of this variable, or the significance it had on their perception of clinical outcomes.

Women connect intimately to the pregnancy experience and often function as information seekers (Lagan et al. 2010), while fathers may take a more passive and subordinate role (Sandelowski & Barroso 2005). Men may not attend prenatal appointments and often learn CMA results from their wives (who were first told the results over the phone) rather than directly from providers. Such gendering of knowledge may account, in part, for the discrepancies observed between women and men. This, however, limits couples' ability to equally contribute to informed decision making about the pregnancy, expectations of the fetus' health, and role as parents (Werner-Lin et al. 2015).

Participants varied in levels of concern about their CMA findings. Interestingly, concern was often unrelated to the lab's classification of pathogenicity. Without guidelines for reporting and interpreting prenatally diagnosed CNVs, what one lab reports as a "likely benign" may be reported as a "variant of uncertain significance" in another (Martin et al. 2015). Furthermore, rare CNVs may be reclassified once evidence mounts (Faas 2015), making providers hesitant to emphasize potentially mutable information. Interpretation of the clinical implications of CNVs also relies on data collected from children and adults with behavioral or neurocognitive deficits (Kearney et al. 2011). Consequently, data likely suffers from ascertainment bias, skewing it towards the severe end of the phenotypic spectrum.

Patient and partner concern was moderated by five factors, including the pattern of inheritance (inherited or *de novo*) of the CNV detected, the range of possible phenotypes, perceived manageability, the strength of evidence available, and messages given by

providers. Participants who initially understood their results as abnormal or uncertain were relieved to learn an apparently normal parent carried the same CNV. Such an interpretation is consistent with research suggesting parents interpret findings to relieve anxiety, establish normalcy in their pregnancy narrative (Werner-Lin et al. 2015) and assuage dissonance (Semaka et al. 2013). Although inherited CNVs may be less likely to pose risk than *de novo* CNVs (Martin et al. 2015), interpreting an inherited variant as benign is potentially problematic because risk may still be heightened since CNVs inherited from an apparently normal parent may affect offspring differently (Costain 2015; Finucane et al. 2015; Lowther et al. 2015). A parent may also be unaware they are subtly phenotypically affected and the CNV could affect their offspring more severely (Martin et al. 2015).

After participants received positive CMA results and collected information, they assessed the extent to which they felt capable of parenting a child with phenotypic involvement. They imagined the best and worst case outcomes, personal values, as well as their expectations, capabilities, and limitations as parents, to make decisions about pregnancy termination (Sandelowski & Barroso 2005). In light of this highly individualized process and the limited window to terminate, an accurate understanding of risk is vital. Consistent with previous research, participants who believed they had resources to identify and manage problems early were more confident in proceeding with their pregnancy (McCoyd 2008; Pieters et al. 2011).

Participants discussed challenges associated with lack of information about their fetus's CNV, as well as lack of probabilistic information about likelihood of a problem manifesting. Variable expressivity and penetrance create a broad range of uncertainty in many positive results, not just VUS results. For example, in the case of the 15q11.2 (BP1-BP2) microdeletion, phenotype ranges from apparently normal to learning deficits, behavioral issues, autism, and seizures (Cox & Butler, 2015). The lack of clear evidence suggesting the CNV would affect the child reassured some participants. Unlike the three where the pathogenicity of the CNV was clear, these participants chose to focus on the real possibility their child might be unaffected, leading to limited or no concern about outcome. Individuals' personality may influence degree of concern; those who are more optimistic may focus on the positive aspects of uncertainty and worry less, as opposed to those lower in optimism (Taber et al., 2015).

Other participants experienced the lack of information as their key source of worry. Participants sought probabilities to quantify risk, and expressed frustration with clinicians who could not offer information. Yet even with quantified risk estimates, patient's health literacy can affect their understanding and interpretation of results, especially when results are ambiguous (Hanoch et al. 2014). Research on other types of genetic testing shows a range of interpretations and reactions to uncertain genetic findings with the frequent use of heuristics consistent with participant's beliefs and experiences to reduce uncertainty (Cypowyj et al. 2009; Semaka et al. 2013).

Our findings indicate participants' level of concern about the impact of CMA results was influenced by overt and implicit provider messages. Although genetic counselors are trained to be non-directive, assisting patients deciding about pregnancy termination in the face of

uncertain results is frequently difficult.(Bernhardt et al. 2014; Mikhaelian et al. 2013) Participants in this study described provider messages of reassurance, particularly with inherited CNVs. When faced with results of uncertain significance, providers frequently tell patients there may be nothing to worry about (Pilnick & Zayts 2014), and patients are likely to interpret and act on providers' preferences (Muller & Cameron 2015). We hypothesize providers may focus less on unknown or potential risks and instead seek to reassure parents who have expressed their desire to continue with a pregnancy. Although providers may be trying to comfort patients and limit their anxiety, it is important for patients to accurately understand potential risk associated with their findings.

## Study Limitations

The present study is one of the first exploring how patients and their partners understand, interpret, and act on prenatal CMA results. Our findings, however, are not generalizable because participants were demographically homogenous and nearly all had achieved high levels of education. We were only able to recruit two women who terminated pregnancies based on CMA results, and only one of these participants' partners completed an interview. It is possible that patients who were more distressed were more likely to seek additional discussion and thus may have been over represented in this study. Since interviews were conducted retrospectively, we could only compare participants' reports of CMA results to laboratory reports and not to actual provider descriptions and discussion of possible phenotypic involvement. The time between participants receiving CNV results and being interview varied considerably and this may have impacted recall. Additionally, although there were few instances where it was clear that participants were consulting the laboratory report during the interview, we cannot be sure that other participants did not have their lab report accessible during the interview.

## Practice Implications

We recommend providers encourage patients and their partners to attend genetic counseling sessions together. This will support discussions with both members of the couple about how much genetic information is desired, the nature and possibility of uncertain information, and decisions about testing and acting on results. Couples often proceed with genetic testing seeking reassurance, without consideration of the possibility of discovering positive or uncertain results. Pre-test counseling should prepare families by clearly outlining the potential for uncertain findings (Reiff et al, 2012). While the provision of information is necessary, alone it is insufficient to support informed consent, comprehension, or decision making. We therefore recommend providers evaluate comprehension throughout the genetic testing process, provide relevant information and clarify misconceptions. Then, if a positive finding is identified, we recommend providers address emotional content openly and directly to prepare families for the psychosocial impact of decisions they will have to make regarding their pregnancy (Werner-Lin, McCoyd & Bernhardt, under review).

Incorporating a teach-back method may help providers to assess and identify gaps in understanding. Such an approach invites patients in a non-judgmental way to describe new or complex concepts following provider explanations so that the provider can check for accuracy and correct misunderstandings. This method has demonstrated improved

information retention and understanding (White et al. 2013; Kaphingst et al., 2009), especially among those with low health literacy (Kripalani et al. 2008), including improved literacy of genetic information

When available, providers should direct patients towards reliable resources (Reiff et al. 2012) that would enable patients to secure information beyond the clinic setting (Haga et al. 2014). Patient also frequently use online resources such as Google and Facebook to seek information and support (Roche & Skinner 2009), and providers should make explicitly sure patients understand what to search for. Also, formal laboratory reports are often difficult for patients to understand. The inclusion of a patient-friendly coversheet detailing results could support accuracy in understanding and recall (Haga et al. 2014; Nielson-Bohlman et al. 2004). Men, in particular, may benefit from such a resource as well as invitations to contact providers directly with questions or concerns.

Last, to accurately convey information associated with specific CNVs, clinicians must understand and be able to explain the terminology associated with genetic variants (e.g. penetrance vs. variable expressivity), and be comfortable discussing uncertain outcomes. In the cases were providers have limited experience counseling about uncertain CNV results, referral to clinicians with more experience is recommended.

### Research recommendations

Future research is needed that observes pre-test genetic counseling sessions and results disclosure sessions to examine how testing and results are discussed with patients and their partners, as well as the effect of having both the patient and her partner present. Additionally, it is especially important to consider how patients make informed decisions when facing uncertain results and how genetic counselors can support them. We also recommend research to assess the extent to which patient friendly reports improve understanding (Haga 2014). Lastly, it is important to include a more diverse group of participants in this type of research.

## Conclusions

As advanced methods of interrogating fetal DNA become more widely applied in diagnostic testing, providers will be called upon to help families understand the potential for intrafamilal variability, as well the spectrum of phenotypes associated with any given variant. Our study emphasizes the need to clearly convey the nature and implications of specific CNVs in a meaningful way so parents can make decision about how to use this information.

## Acknowledgements

This work was supported by funding from the National Institute of Child Health and Development, National Institutes of Health (UO1-HD-055651). There was no additional involvement from funding sources.

## References


Alsulaiman A, Hewison J, Abu-Amero KK, Ahmed S, Green JM, Hirst J. Attitudes to prenatal diagnosis and termination of pregnancy for 30 conditions among women in Saudi Arabia and the UK. Prenatal Diagnosis. 2012; 32:1109–1113. doi:10.1002/pd.3967. [PubMed: 22945692]

American College of Obstetricians and Gynecologist. Committee opinion no. 581: the use of chromosomal microarray analysis in prenatal diagnosis. Obstetrics and Gynecology. 2013; 122:1374–1377. doi:10.1097/01.AOG.0000438962.16108.d1. [PubMed: 24264715]

Bernhardt BA, Kellom K, Barbarese A, Faucett WA, Wapner RJ. An exploration of genetic counselors' needs and experiences with prenatal chromosomal microarray testing. Journal of Genetic Counseling. 2014; 23:938–947. doi:10.1007/s10897-014-9702-y. [PubMed: 24569858]

Bernhardt BA, Soucier D, Hanson K, Savage MS, Jackson L, Wapner RJ. Women's experiences receiving abnormal prenatal chromosomal microarray testing results. Genetics in Medicine. 2013; 15:139–45. doi:10.1038/gim.2012.113. [PubMed: 22955112]

Costain G. Parental expression is overvalued in the interpretation of rare inherited variants. European Journal of Human Genetics. 2015; 23:4–7. doi:10.1038/ejhg.2014.64. [PubMed: 24755951]

Cox DM, Butler MG. The 15q11.2 BP1-BP2 microdeletion syndrome: a review. International Journal of Molecular Sciences. 2015; 16:4068–4082. doi:10.3390/ijms16024068. [PubMed: 25689425]

Crolla JA, Wapner R, Van Lith JMM. Controversies in prenatal diagnosis 3: should everyone undergoing invasive testing have a microarray? Prenatal Diagnosis. 2014; 34:18–22. doi: 10.1002/pd.4287. [PubMed: 24302430]

Cypowyj C, Eisinger F, Huiart L, Sobol H, Morin M, Julian-Reynier C. Subjective interpretation of inconclusive BRCA1/2 cancer genetic test results and transmission of information to the relatives. Psycho-Oncology. 2009; 18:209–15. doi:10.1002/pon.1407. [PubMed: 19061202]

Faas BH. Prenatal genetic care: debates and considerations of the past, present and future. Expert Opinion on Biological Therapy. 2015; 15:1101–1105. doi:10.1517/14712598.2015.1045873. [PubMed: 25959656]

Finucane B, Challman TD, Martin CL, Ledbetter DH. Shift happens: family background influences clinical variability in genetic neurodevelopmental disorders. Genetics in Medicine. 2015 doi: 10.1038/gim.2015.92.

Haga SB, Mills R, Pollak KI, Rehder C, Buchanan AH, Lipkus IM, Datto M. Developing patient-friendly genetic and genomic test reports: formats to promote patient engagement and understanding. Genome Medicine. 2014; 6:58. doi:10.1186/s13073-014-0058-6. [PubMed: 25473429]

Hanoch Y, Miron-Shatz T, Rolison JJ, Ozanne E. Understanding of BRCA1/2 genetic tests results: the importance of objective and subjective numeracy. Psycho-Oncology. 2014; 23:1142–1148. doi: 10.1002/pon.3537. [PubMed: 24733657]

Hillman SC, Willams D, Carss KJ, McMullan DJ, Hurles ME, Kilby MD. Prenatal exome sequencing for fetuses with structural abnormalities: the next step. Ultrasound in Obstetrics & Gynecology. 2015; 45:4–9. doi:10.1002/uog.14653. [PubMed: 25157891]

Kaphingst KA, Lachance CR, Gepp A, Hoyt D'Anna L, Rios-Ellis B. Educating underserved Latino communities about family health history using lay health advisors. Public Health Genomics. 2009; 14(4-5):211–221. doi: 10.1159%2F000272456. [PubMed: 20051669]

Kearney HM, Thorland EC, Brown KK, Quintero-Rivera F, South ST. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. Genetics in Medicine. 2011; 13:680–685. doi:10.1097/GIM.0b013e3182217a3a. [PubMed: 21681106]

Kiedrowski LA, Owens KM, Yashar BM, Schuette JL. Parents' perspectives on variants of uncertain significance from chromosome microarray analysis. Journal of Genetic Counseling. 2015 doi: 10.1007/s10897-015-9847-3.

Kripalani S, Bengtzen R, Henderson LE, Jacobson TA. Clinical research in low-literacy populations: using teach-back to assess comprehension of informed consent and privacy information. IRB. 2008; 30:13–19. doi: 10.1007/s10865-015-9642-5. [PubMed: 18512655]

Lagan BM, Sinclair M, Kernohan WG. Internet use in pregnancy informs women's decision making: a web-based survey. Birth. 2010; 37:106–115. doi:10.1111/j.1523-536X.2010.00390.x. [PubMed: 20557533]

Nielson-Bohlman, L.; Panzer, A.; Kindig, D. Health literacy: a prescription to end confusion. National Academic Press; Washington, DC.: 2004.

Lowther C, Costain G, Bassett AS. Reproductive genetic testing and human genetic variation in the era of genomic medicine. The American Journal of Bioethics. 2015; 15:25–26. doi: 10.1080/15265161.2015.1028661. [PubMed: 26030491]

Martin CL, Kirkpatrick BE, Ledbetter DH. Copy number variants, aneuploidies, and human disease. Clinics in Perinatology. 2015; 42:227–242. doi:10.1016/j.clp.2015.03.001. [PubMed: 26042902]

McCoyd J. “I'm not a saint”: burden assessment as an unrecognized factor in prenatal decision making. Qualitative Health Research. 2008; 18:1489–1500. doi:10.1177/1049732308325642. [PubMed: 18849510]

Miles, MB.; Huberman, AM. An expanded sourcebook. 2nd ed.. Sage Publications, Inc.; Thousand Oaks, CA: 1994. Qualitative data analysis.; p. 55-103.

Mikhaelian M, Veach PM, MacFarlane I, LeRoy BS, Bower M. Prenatal chromosomal microarray analysis: a survey of prenatal genetic counselors' experiences and attitudes. Prenatal Diagnosis. 2013; 33:371–377. doi:10.1002/pd.4071. [PubMed: 23450520]

Muller C, Cameron LD. It's complicated: factors predicting decisional conflict in prenatal diagnostic testing. Health Expectations. 2015 doi: 10.1111/hex.12363.

Nahar R, Puri RD, Saxena R, Verma IC. Do parental perceptions and motivations towards genetic testing and prenatal diagnosis for deafness vary in different cultures? American Journal of Medical Genetics. 2013; 161A:76–81. doi:10.1002/ajmg.a.35692. [PubMed: 23208825]

Norton ME, Nakagawa S, Kuppermann M. Women's attitudes regarding prenatal testing for a range of congenital disorders of varying severity. Journal of Clinical Medicine. 2014; 3:144–152. doi: 10.3390/jcm3010144. [PubMed: 26237253]

Pieters JJ, Kooper AJ, Eggink AJ, Verhaak CM, Otten BJ, Braat DD, van Leeuwen E. Parents' perspectives on the unforeseen finding of a fetal sex chromosomal aneuploidy. Prenatal Diagnosis. 2011; 31:286–292. doi:10.1002/pd.2707. [PubMed: 21294136]

Pilnick A, Zayts O. “It's just a likelihood”: uncertainty as topic and resource in conveying “positive” results in an antenatal screening clinic. Symbolic Interaction. 2014; 37:187–208. doi:10.1002/symb.99.

Reiff M, Bernhardt BA, Mulchandani S, Soucier D, Cornell D, Pyeritz RE, Spinner NB. “What does it mean?”: uncertainties in understanding results of chromosomal microarray testing. Genetics in Medicine. 2012; 14:250–258. doi:10.1038/gim.2011.52. [PubMed: 22241091]

Reiff M, Giarelli E, Bernhardt BA, Easley E, Spinner NB, Sankar PL, Mulchandani S. Parents' perceptions of the usefulness of chromosomal microarray analysis for children with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2015; 45:3262–3275. doi: 10.1007/s10803-015-2489-3. [PubMed: 26066358]

Richards EG, Sangi-Haghpeykar H, McGuire AL, Van den Veyver IB, Fruhman G. Pregnant patients' risk perception of prenatal test results with uncertain fetal clinical significance: ultrasound versus advanced genetic testing. Prenatal Diagnosis. 2015 doi:10.1002/pd.4680.

Roche MI, Skinner D. How parents search, interpret, and evaluate genetic information obtained from the internet. Journal of Genetic Counseling. 2009; 18:119–129. doi:10.1007/s10897-008-9198-4. [PubMed: 18937062]

Sandelowski M, Barroso J. The travesty of choosing after positive prenatal diagnosis. Journal of Obstetric, Gynecologic, and Neonatal Nursing. 2005; 34:307–318. doi: 10.1177/0884217505276291.

Semaka A, Balneaves LG, Hayden MR. “Grasping the grey”: patient understanding and interpretation of an intermediate allele predictive test result for Huntington disease. Journal of Genetic Counseling. 2013; 22:200–217. doi:10.1007/s10897-012-9533-7. [PubMed: 22903792]

Taber JM, Klein WMP, Ferrer RA, Han PKJ, Lewis KL, Biesecker LG, Biesecker BB. Perceived ambiguity as a barrier to intentions to learn genome sequencing results. Journal of Behavioral Medicine. 2015; 38:715–726. doi:10.1007/s10865-015-9642-5. [PubMed: 26003053]

Turbitt E, Halliday JL, Amor DJ, Metcalfe SA. Preferences for results from genomic microarrays: comparing parents and health care providers. Clinical Genetics. 2015; 87:21–29. doi:10.1111/cge.12398. [PubMed: 24773164]

Van der Steen SL, Diderich KE, Riedijk SR, Verhagen-Visser J, Govaerts LC, Joosten M, Galjaard RJ. Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing. Clinical Genetics. 2015; 88:25–31. doi:10.1111/cge.12479. [PubMed: 25134982]

Walser SA, Kellom KS, Palmer SC, Bernhardt BA. Comparing genetic counselor's and patient's perceptions of needs in prenatal chromosomal microarray testing. Prenatal Diagnosis. 2015; 35:870–878. doi:10.1002/pd.4624. [PubMed: 25995037]

Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, Jackson L. Chromosomal microarray versus karyotyping for prenatal diagnosis. The New England Journal of Medicine. 2012; 367:2175–2184. doi:10.1056/NEJMoa1203382. [PubMed: 23215555]

Werner-Lin A, Barg FK, Kellom KS, Stumm KJ, Pilchman L, Tomlinson AN, Bernhardt BA. Couple's narratives of communion and isolation following abnormal prenatal microarray testing results. Qualitative Health Research. 2015 doi:10.1177/1049732315603367.

Werner-Lin A, McCoyd J, Bernhardt B. Recommendations for psychosocial genetic counseling during prenatal cytogenetic microarray analysis: Addressing uncertainty with more than just information. under review.

White M, Garbez R, Carroll M, Brinker E, Howie-Esquivel J. Is “teach-back” associated with knowledge retention and hospital readmission in hospitalized heart failure patients? The Journal of Cardiovascular Nursing. 2013; 28:137–146. doi:10.1097/JCN.0b013e31824987bd. [PubMed: 22580624]

Willis AM, Smith SK, Meiser B, Muller C, Lewis S, Halliday J. How do prospective parents prefer to receive information about prenatal screening and diagnostic testing? Prenatal Diagnosis. 2015; 35:100–102. doi:10.1002/pd.4493. [PubMed: 25196282]

## Table 1

Description of participants

| Participant Characteristics | Patient (N=28) | Partner (N=12) |
|---|---|---|
| Average age (years) | 35 | 36 |
| Age range | 20-43 | 29-46 |
| Highest education achieved | | |
| Professional / doctoral degree (MD, PhD, etc.) | 6 | 3 |
| Master's degree | 7 | 3 |
| Bachelor/ Associates degree | 13 | 5 |
| High school diploma | 2 | 1 |
| Race* | | |
| White | 24 | 11 |
| Black | 1 | 0 |
| Asian | 4 | 0 |
| Hispanic/ Latino | 2 | 1 |
| Religious affiliation | | |
| Catholic | 4 | 6 |
| Protestant | 3 | 1 |
| Jewish | 7 | 2 |
| No religious affiliation | 12 | 1 |
| Other religious affiliation | 2 | 1 |
| Unknown | 0 | 1 |
| Pregnancy History | (N=28) | |
| Procedure performed | | |
| Amniocentesis | 14 | |
| Chorionic villus sampling (CVS | 11 | |
| Both | 3 | |
| Reason for receiving prenatal testing* | | |
| Advanced maternal age | 14 | |
| Family history of genetic abnormality | 3 | |
| Chromosomal abnormality in previous pregnancy | 4 | |
| Increased risk based on first trimester blood test | 5 | |
| Abnormal second trimester ultrasound | 6 | |
| Other | 1 | |
| Elected terminations | 2 | |

*Could select more than one answer

## Table 2

Themes and illustrative quotes relating to description of results

| Theme | Illustrative quote |
|---|---|
| **Type of result (deletion, duplication, mosaicism)** | |
| **Correct (n=28 women, 8 men)** | *"we've got the results of this like duplication"*<br>*"there was a micro deletion"* |
| **Incorrect/ unsure/ not mentioned (n= 0 women, 3 men)** | *"there was some grey area"*<br>*"there was an abnormal finding"* |
| **Chromosome involved or disorder** | |
| **Correct (n=24 women, 6 men)** | *"It's a 15q11"*<br>*"...tested positive for Beckwith-Wiedemann"*<br>*"the issue was the DiGeorge"* |
| **Incorrect/ unsure/ not mentioned (n= 4 woman, 6 men)** | *"but it was a micro deletion...I forgot which one"*<br>*"I'm not sure if it was a chromosome or what the issue was"* |
| **Inheritance (inherited/ de novo)** | |
| **Correct (n=28 women, 12 men)** | *"the two anomalies that showed up on the fetus were both inherited"*<br>*"one inherited from my husband and one de novo"*<br>*"Unfortunately for us we were both negative"* |
| **Incorrect/ unsure/ not mentioned (n=0)** | — |

**Table 3**

Concern about impact of findings on fetus

| Level of concern | Illustrative quotes |
|---|---|
| **Significantly concerned (n= 2 women, 1 man)** | *"I know what it looks like and it looks horrible"*<br>*"It was just a really, really grim outlook"* |
| **Somewhat concerned (n= 11 women,5 men)** | *"Those guys gave me the comfort to go forward, although it's still higher risk"*<br>*We're prepared for the worst possible thing to happen and if it doesn't –great, but if it does, we're prepared for it"* |
| **Lingering concern (n=6 women, 1 man)** | *"We all felt comfortable that it would probably be okay"*<br>*"It probably won't have any clinical significance to her, since we don't have any..."* |
| **Not concerned (n=9 women, 5 men)** | *"it was no big deal when we got the results...not even second thinking it"*<br>*"Because my husband had it, it was okay"*<br>*"There could be a chance that (other son) had it too and he's fine. So once she told me that, I didn't worry about it after that"* |

## Table 4

Characteristics of CMA findings and outcome

| Pregnancy | Lab classification of CNV* | Inheritance of CNV on lab report | Patient's concern about outcome | Partner's concern about outcome | Pregnancy outcome |
|---|---|---|---|---|---|
| **313** | pCNV | Unknown | Somewhat concerned | — | Continuing |
| **202** | pCNV | *De novo* | Significantly concerned | Significantly concerned | Terminated |
| **201** | pCNV | *De novo* | Significantly concerned | — | Terminated |
| **306** | lpCNV | *De novo* | Somewhat concerned | Somewhat concerned | Continuing |
| **315** | uCNV | Inherited | Lingering doubt | — | Continuing |
| **304**** | uCNV / uCNV | Inherited / *de novo* | Somewhat concerned | — | Continuing |
| **301**** | uCNV / uCNV | Inherited / Inherited | Somewhat concerned | Not concerned | Continuing |
| **101**** | uCNV / uCNV | Inherited/inherited | Somewhat concerned | Somewhat concerned | Continuing |
| **319** | uCNV | Unknown | Lingering doubt | Not concerned | Continuing |
| **318** | uCNV | *De novo* | Somewhat concerned | — | Continuing |
| **309** | uCNV | Unknown | Lingering doubt | Somewhat concerned | Continuing |
| **308** | uCNV | Unknown | Not concerned | — | Continuing |
| **303** | uCNV | Inherited | Not concerned | — | Continuing |
| **109** | uCNV | Unknown | Somewhat concerned | Somewhat concerned | Continuing |
| **108** | uCNV | Unknown | Somewhat concerned | — | Continuing |
| **103** | uCNV | Inherited | Not concerned | Not concerned | Continuing |
| **310** | lbCNV | Inherited | Not concerned | — | Continuing |
| **312** | lbCNV | Inherited | Lingering doubt | — | Continuing |
| **302** | lbCNV | Unknown | Not concerned | — | Continuing |
| **300** | lbCNV | Inherited | Not concerned | Lingering doubt | Continuing |
| **111** | lbCNV | Inherited | Somewhat concerned | — | Continuing |
| **106** | lbCNV | Inherited | Not concerned | — | Continuing |
| **105** | lbCNV | Inherited | Lingering doubt | — | Continuing |
| **104** | lbCNV | Inherited | Somewhat concerned | Not concerned | Continuing |
| **107***** | lbCNV | Inherited | Not concerned | — | Selective reduction of twin A |
| **307** | Not available | Unknown | Not concerned | Not concerned | Continuing |
| **114** | Not available | Unknown | Lingering doubt | — | Continuing |
| **112***** | Not available | Unknown | Somewhat concerned | Somewhat concerned | Continuing |

* pCNV = pathogenic CNV; lpCNV = likely pathogenic CNV; uCNV = variant of uncertain significance; lbCNV = likely benign CNV

** Two CNVs identified

*** Carrying multiples

## Table 5

Illustrative quotes relating to moderators of participant concern about impact of findings on fetus

| Themes | Illustrative quote |
|---|---|
| **Type of involvement** | *"There's typically heart failure somewhere along the line, whether that's earlier or later."*<br>*"So you know, we don't care if the kid looks a little odd or needs a couple of plastic surgeries. If there's one thing—residual thing—that's a source of anxiety is the cancer risk."* |
| **Strength of evidence** | *"I wasn't too worried because they said that they don't know any clinical significance to it yet. It didn't necessarily mean anything bad. Not knowing anything was better than bad news."*<br>*"To be told 'we don't even have any statistics at all' and that 'the people who have this disorder—some have a heart problem, some don't; some are tiny, some are big; some of them are really smart, some of them can't speak at all'"* |
| **Inheritance** | *"The worst are obviously the ones that are de novo or just happen...versus being hereditary, because if it just happens, you can't prove what the outcome is, where if I'm a carrier you can see if I'm a functioning human being."*<br>*"I feel like I'm pretty normal. I'm hoping that whatever that it is just like some kind of a 'passed down' thing from my family or something that isn't gonna affect him, like it didn't affect me."* |
| **Manageability** | *"It's not something that's gonna affect the child's cognition or life span or health ultimately. It seems that it is something that is very easily treated, it's just the treatment is pretty expensive."*<br>*"It's really a big gamble and there's no answer as to how each child is gonna react from the surgeries... the life expectancy normally isn't very high."* |
| **Provider message** | *"The geneticist said 'send me pictures when the baby's born'—that was her way of saying it's good to go."*<br>*"[The doctors said] 'look, you're healthy, you're human, this happens all the time. You're a functioning adult; a lot of genes—just junk genes—they just take up space.'"*<br>*"He said 'you don't want to do this. This is just going to be tragedy for you and your husband and the baby.' I just trusted him so much and they were just so clear, that the problems that were on their way if we chose not to terminate."* |