[Cult Med Psychiatry](#). 2017 Sep;41(3):382-406. doi: 10.1007/s11013-017-9521-3.

Expert Knowledge Influences Decision-Making for Couples Receiving Positive Prenatal Chromosomal Microarray Testing Results

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Keywords: Microarray, Prenatal Testing, Uncertainty, Expert Knowledge, Decision-Making

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Statement of originality: This submission is the authors' original research, and it has not been submitted or published elsewhere.

Acknowledgements: This work was supported by funding from the National Institute of Child

Health and Development, National Institutes of Health (UO1-HD-055651). Thank you to Katherine Kellom, Kallyn Stumm, and Lisa Pilchman for their work in collecting data toward this paper and to Sarah Walser for preparation of the manuscript. MAR wishes to thank Evan Anderson and Katherine Culver for their helpful manuscript comments in addition to Aaron Pollock, Andrew Buck, and Tara Retson for project advice.

ABSTRACT

To assess how participants receiving abnormal prenatal genetic testing results seek information and understand the implications of results, 27 US female patients and 12 of their male partners receiving positive prenatal microarray testing results completed semi-structured phone interviews. These interviews documented participant experiences with chromosomal microarray testing, understanding of and emotional response to receiving results, factors affecting decision-making about testing and pregnancy termination, and psychosocial needs throughout the testing process. Interview data were analyzed using a modified grounded theory approach. In the absence of certainty about the implications of results, understanding of results is shaped by biomedical expert knowledge (BEK) and cultural expert knowledge (CEK). When there is a dearth of BEK, as in the case of receiving results of uncertain significance, participants rely on CEK, including religious/spiritual beliefs, “gut instinct,” embodied knowledge, and social network informants. CEK is a powerful platform to guide understanding of prenatal genetic testing results. The utility of culturally situated expert knowledge during testing uncertainty emphasizes that decision-making occurs within discourses beyond the biomedical domain. These forms of “knowing” may be integrated into clinical consideration of efficacious patient assessment and counseling.

INTRODUCTION

Utilization of prenatal genetic testing has increased due to rising public acceptance (Allyse et al. 2014), biomedical endorsement (Norton et al. 2012), and decreasing costs (Community Corner: Opening the Pandora's Box of Prenatal Genetic Testing 2011). Prospective parents can now choose among various types of invasive (i.e., amniocentesis and chorionic villus sampling), non-invasive (i.e., cell-free fetal DNA, ultrasound), and integrated screening (maternal serum markers and nuchal translucency combined) that provide varied levels of evidence of a fetal anomaly or genetic condition (for a more detailed review, see: (de Jong, Maya, and van Lith 2015). Utilization of prenatal genetic testing by prospective parents who view this testing as an accessible, routine, and desirable component of prenatal care may yield findings associated with severe disorders, syndromes of variable severity and age of onset, and results with uncertain clinical significance (Kaminsky et al. 2011). The difficulty in robustly correlating some genetic variants with phenotypic outcomes complicates decision-making for couples trying to decide if the fetus is likely to be “healthy” and “normal” when presented with a choice to continue or terminate a pregnancy.

Chromosomal microarray, referred to here as prenatal microarray, is a type of prenatal testing that is increasingly utilized to detect copy-number variants not detectable by conventional cytogenetics. In a recent multicenter study of 3000 women having prenatal microarray testing for routine indications, 0.9% of cases indicated a pathogenic copy-number variants, 1.8% showed a copy-number variants that was likely benign, and 1.6% of cases had a copy-number variants that was a variant of uncertain significance (VUS) (Wapner et al. 2012). The American College of Obstetrics and Gynecology recommends prenatal microarray testing if a fetal structural anomaly

is diagnosed on ultrasound, and advises that the test be offered to women having invasive testing (amniocentesis or CVS) for any indication (The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis - ACOG 2013). Interestingly, in a study of Dutch couples undergoing routine invasive prenatal testing, the majority would choose microarray in conjunction with or instead of conventional methods such as karyotyping, even with the increased probability of receiving a VUS result (Riedijk et al. 2014).

Despite informed consent practices that disclose the risk of uncertain results prior to microarray testing, prospective parents have reported feeling anxious and overwhelmed after receiving a VUS result (Bernhardt et al. 2013). Couples must then navigate a nebulous decision making path regarding whether to continue or terminate a pregnancy, often assuming gendered responsibilities in the process (Werner-Lin et al. 2015). The degree to which individuals find, believe, and utilize various sources of information is a function of variables such as ethnicity (Guidry et al. 1998; Kakai et al. 2003; Rooks et al. 2012), gender (Halder, Ray, and Chakrabarty 2010), age (Turk-Charles, Meyerowitz, and Gatz 1997), socioeconomic status (Calvert, Aidala, and West 2013; Ramanadhan and Viswanath 2006), education (Carlsson 2014; Tu and Cohen 2008), and religious and spiritual beliefs (Cadge and Bergey 2013; Matthews et al. 2002), and may be further stratified by information seeking tendencies (Anker, Reinhart, and Feeley 2011; Wallston, Maides, and Wallston 1976). These alternate knowledge platforms move beyond biomedically validated information into social and cultural forms of knowledge that individuals and couples can draw from and negotiate with each other to make and validate pregnancy decisions.

Biomedical Expert Knowledge

Biomedical expert knowledge (BEK), drawn from a western biomedical paradigm and defined here as knowledge from clinicians (doctors, genetic counselors), scholarly literature (medical internet databases, journals), and general knowledge from “within” the biomedical expert system, has been widely acknowledged as occupying a privileged status (McCoyd 2010). Although BEK is seen as separate from social and cultural domains, it arises from, and is deeply embedded within, social and cultural conditions (Lock and Gordon 1988). BEK is characterized by a biological reductionism; that aspects of the patient’s body and its symptoms are variables that can be independently and objectively evaluated and treated. BEK’s broad acceptance in western medical systems is produced and reified from its effectiveness, emphasis on patient autonomy, and “naturalness” of its object of study (Browner and Press 1997; Davis-Floyd 2001; Jordan 1997; Wright and Treacher 1982).

Although it is itself a cultural construction, BEK is routinely considered separately from the cultural domain, and this separation imbues it with an empirical legitimacy and objective validity (Rhodes 1990; Sargent and Bascope 1997; Scheper-Hughes 1990; Taylor 2003). Findings from a study of over 6,000 US patients showed that even with the availability of online resources, patients placed substantial trust in physician-derived knowledge (Hesse et al. 2005). Furthermore, the majority of men and women in western biomedical frameworks prefer advice from authoritatively legitimated health care providers rather than from media such as the internet (Fox 2011; Hu et al. 2012; Pennbridge, Moya, and Rodrigues 1999). The degree of dichotomization between biomedical and cultural explanatory models for health and illness is entirely context dependent; for example, medical knowledge is incorporated to varying extents with popular and folk medical systems in countries with pluralistic medical traditions (Lock 1980; Low 1988; Maretzki and Seidler 1985). Within the U.S., however, BEK frequently abuts

against alternative forms of expert knowledge, such as “embodied,” “folk,” or “cultural” knowledge. The very nature of these forms of cultural knowing as unique, dynamic, and situation-relevant makes them resistant to empirical quantification and thus incorporation into a biomedical paradigm.

Beyond the Biomedical

The “new genetics” presents prospective parents with the opportunity to interrogate the genome beyond our capacity to interpret some findings within the biomedical paradigm (Bernhardt et al. 2013; Ormond and Cho 2014; Lock 2005). In the absence of BEK, individuals with ambiguous information facing critical decisions may seek out other authoritative voices to augment understanding, and it is in this space that other forms of knowing gain authority. Some forms of knowledge may be given precedence depending on explanatory value, structural superiority (a stronger power base), or, more often, some combination of the two (Jordan 1997; Prior 2003; McCoyd 2010; Skinner, Raspberry, and King 2016). In situations with multiple potential knowledge frameworks, one kind of expert or authoritative knowledge is often legitimated and the other devalued or dismissed (Pols 2013); for example, subjectively derived medical knowledge is considered “backward” and “ignorant” within the domain of western biomedicine (Jordan, 1997).

Variability and uncertainty are common features of prenatal testing. The possibility of a VUS often prompts prospective parents to incorporate types of socially and culturally produced expert knowledge, or “other ways of knowing,” to mitigate uncertainty and to direct pregnancy decisions simply because empirically derived information from the biomedical sphere does not yet exist. For example, in narratives of pregnancy, women often possess an embodied,

experiential knowledge about the health of their unborn child and the state of their pregnancy (Browner and Press 1997; Etchegary et al. 2008). Other studies have described the importance of religious or spiritual convictions in determining individual attitudes towards prenatal testing, results, and decisions (Ahmed et al. 2006; Ahmed, Green, and Hewison 2006; Kobelka, Mattman, and Langlois 2009; Leung et al. 2004; Pivetti et al. 2013; Seror and Ville 2010; Seth et al. 2011). Informal stories of pregnancy and childbirth shared among women with similar experiences teach coping mechanisms and can provide information accrual for rarer diagnoses where there is a dearth of formal biomedical information (Lowe 2005). These can be drawn on in medical contexts to ground decision making within a perceived environment of social support (Banks-Wallace 2002; Livo and Rietz 1986). Social network analysis is often used to address this knowledge deficit (Hillman et al. 2013; McKechnie, Pridham, and Tluczek 2014; Atkinson, Featherstone, and Gregory 2013), but is insufficient to capture the broad range of resources needed in such an overwhelming gap in knowledge that has such high consequences, as is the case with receiving a prenatal VUS result. In particular, when there is no familial linkage between a genetic variant and a phenotype, as is the case of a *de novo* VUS, families have increased concern (Walser et al. 2016) and must extend their information search beyond the boundaries of biomedical knowledge.

AIM

This study uses grounded theory methodology to understand the sources of knowledge within and beyond the biomedical domain that prospective parents utilize to generate knowledge for the understanding and management of prenatal microarray results associated with varying degrees of

uncertainty. We investigate how participants used distinct knowledge platforms to give empirical weight and socially validated meaning to pregnancy decisions.

METHODS

This study protocol was approved by the Institutional Review Boards of the University of Pennsylvania and Columbia University. Data were derived from interviews with twenty-seven women and twelve male partners who completed prenatal microarray analysis and received an uncertain or pathogenic microarray result.

Recruitment. Pregnant women receiving care from prenatal testing facilities collaborating with the University of Pennsylvania and Columbia University learned about the study from a pamphlet provided after receiving results from microarray testing. The pamphlet invited any woman who had received prenatal microarray testing results in the past 4-6 weeks to participate in a short online survey. In the survey, women provided demographic information and indicated the type of result (normal, abnormal, or uncertain) they received with the approximate date they received it. We contacted survey respondents who received abnormal or uncertain prenatal microarray results. These participants were asked 1) whether they or their partners carried the same deletion or duplication, 2) whether they were continuing or terminating their pregnancy, and 3) whether they would be interested in hearing about the interview portion of the study.

The study coordinator sent e-mails describing the interview portion to all eligible participants who, on the survey, indicated interest and then scheduled interviews based on the participant's availability. With the participant's permission the researchers obtained a copy of the prenatal microarray laboratory report.

Sample.

Of 152 female patients who completed the survey, 36 (24%) had an abnormal result or a VUS and were eligible to be interviewed. Of these 36, 27 women were interviewed and some of these women indicated that their male partners had interest in participation. A subset of 12 male partners was subsequently interviewed, bringing the total number of interviews to 39. Women ranged in age from 20 to 43 and men from 29 to 46, with the majority of both sexes in the 31-to-40-year-old bracket (74.4%). Nearly all participants identified as white (84.6%), college educated (89.7%), and 64.1% acknowledged a religious affiliation (predominantly Catholic and Jewish) (Table 1, Participant Demographics).

Interviews. Study staff developed a semi-structured interview guide to elicit information from patients and their partners about how they made the decision to have prenatal microarray testing, their experiences receiving results, and their needs throughout the testing process and moving forward. Interviewers probed about how patients understood results and their implications and how comfortable they felt with their decision to continue or terminate the pregnancy. All interviews were conducted over the phone after obtaining verbal consent from the participant. At the end of the interview with the patient, she was asked whether she had a partner whom study staff might invite to participate in an interview. If the patient responded favorably, study staff reached out to the partner to provide information about what participation entailed. After completing an interview, all study participants were sent a \$25 gift card.

Interviews lasted between 30 to 80 minutes, were recorded, and professionally transcribed. Study staff read through the transcribed interviews to check for accuracy, completeness, and to redact any identifiable information. De-identified interviews were imported into QSR International's NVivo 10 software for coding and analysis.

Data management. Data analysis began with line-by-line coding of the first three interview transcripts to identify a preliminary list of codes. These included open and *in vivo* codes that iteratively arose out of participant responses as well as focused codes (Charmaz 2006) addressing “ways of knowing” (Jordan, 1997). Additional *sensitizing concepts* [terms that already existed in the literature, Padgett, 2008], included references to situational or result uncertainty and certainty. Focused coding was also utilized to identify participant interface with clinicians, hospitals, clinics, and scholarly literature from internet databases such as PubMed and medical internet searches, in addition to any other method of information seeking outside these parameters. Following this initial review, the research team met to discuss themes towards the initial development of a codebook.

Following discussion with the research team, the first author created a working codebook listing code definitions and parameters, brief memos, and examples of each code (Table 2: Codes and Definitions). Then, she completed another round of coding to clarify and collapse emerging codes. To facilitate translation of codes into findings, codes were grouped into two categories: (1) biomedical expert knowledge (2) other ways of knowing. Members of the interdisciplinary research team that included seasoned qualitative researchers met regularly to discuss emerging codes, categories and themes; to revise interview guides; and to update the codebook.

FINDINGS

Of the 27 women included in the study, three reported that they received a laboratory-classified pathogenic result and 24 had a VUS result. Within the VUS subgroup, one woman received a “likely pathogenic” result, twelve had “uncertain” results, nine were “likely benign,” and for two, results were not available. (Table 3: Table Prenatal Microarray Results). Of the 24

receiving a VUS result, four reported that the result was *de novo*, thirteen were inherited, and six patients were unsure. One additional case included both a *de novo* and an inherited copy number variant. Two patients elected to terminate the pregnancy, and one woman with a multiple gestation had a selective reduction of one fetus.

Using Biomedical Expert Knowledge to Get Information and Make Decisions

For many patients and partners, the delivery of positive results with uncertain or variable outcomes prompted a state of crisis and the gathering of relevant biomedical knowledge. Participants articulated that BEK was helpful if it positioned them to make decisions. If providers could not offer clear information about the clinical implications of a rare copy number variant, providers often counseled participants to complete further testing and frequently tested the parents to confirm whether the fetal genetic variant was inherited. In another case, the initial microarray identified placental mosaicism on tissue obtained from a CVS. A repeat microarray performed on amniotic fluid cells failed to reproduce the abnormality, solidifying the couple's decision to continue their pregnancy.

During follow-up testing, some clinicians provided participants with additional resources, such as scholarly literature and informational leaflets. Participants also independently pursued medical literature and biomedical websites with varying degrees of success. This affected perceptions of clinical efficacy and trust in the biomedical system. Recalls one patient:

“The doctor is a little better because it's somebody that has some knowledge instead of just Google-ing it, so it made me feel a little more comfortable.”

Entrusting providers to authoritatively disseminate knowledge, rather than independently generate it from alternate BEK sources (i.e., the internet), provided a subset of participants with reassurance.

Perceived or inferred provider opinion was a strong factor in shaping patient confidence when making a decision (i.e., continuing a pregnancy or inducing abortion). One patient recounted the relieved response of medical staff at the announcement of her decision to continue the pregnancy:

“They were so careful to not give us any sort of swaying or anything. They gave us the facts and then said make your own decision. But once we announced what our decision was, it seemed like everyone just agreed with us all at the same time. They were all like ‘Whew, okay we’re so glad’...I’m like ‘What!?’ Why wouldn’t you have said this...that you would be glad if we kept it? They’re like ‘We by law, cannot have an opinion until you make a decision.’”

The passage above underscores the difficulties many providers may experience in maintaining a non-directive position, particularly in face of vague medical outcomes for the unborn child. Another patient recalled her physician requesting pictures after the baby’s birth, which she understood as the physician’s way of endorsing the pregnancy as “good to go.” Another patient attributed the BEK given by and through medical experts with directing her decision:

“They made the decision for me in a very gentle way. [...]I don’t really feel like I had to make the decision by myself. I felt like they laid out just the severity of the issue and then it was just pretty obvious what we needed to do.”

When a decision was achieved through utilization of some form of BEK, patients and their partners were able to resolve a significant portion of their situational uncertainty and concomitant anxiety. As one participant recalled:

“We got another ultrasound done and then we sat with a doctor and a counselor—and that was very helpful. That I think, more than the research on my end, kind of gave us closure and gave us the information that we needed to make a decision.”

Accruing BEK Online: Information-Seeking Participants

Participants accepted BEK when it resolved situational uncertainty and informed decisions. They also independently accrued BEK, or drew information from BEK not directly provided by a clinician, and incorporated various other ways of knowing to make decisions. Suggestions for websites provided by clinicians gave participants a suite of resources to access on their own time; however, most participants expressed frustration that they did not receive as much of this information as they would have liked. Many participants felt that they could have handled complex literature and online material of a technical nature. Several participants acknowledged education or career background in legitimating their ability to overcome the “gap” between what they knew (the test results) and what they wanted to know to achieve a decision (i.e., what the test results mean):

“We're highly educated people, so my husband and I were able to deal with scoping through what seemed to be more like valid, scientific studies or not, and understand-the general gist of what they were saying. Through that we felt that we could get a better handle on it than just talking to the genetic counselor.”

Participants who felt like the amount and quality of BEK were not satisfying their information “gap” experienced frustration and lost confidence in clinicians to provide further information.

“It would be nice if my maternal-fetal doctor-knew anything about the disorder or cared enough to Google it for ten seconds before meeting with me.”

Given the scope of potential outcomes for some genetic results, participants were exceedingly resourceful and invested significant time and effort into pursuing “independently” derived sources of BEK when authoritative sources could no longer provide answers. They conducted online research, joined professional support and information groups, and contacted other clinicians and geneticists. One patient recounted of her conversation with her doctor:

“I asked him for a copy of every single problem that it screens for and then I did research to find out what all those things were and that's fifteen pages of disorders and I looked them all up.”

Participants sought additional BEK because they believed their biomedical providers could not be of further help in the decisional process. One prospective father discussed how his independently derived BEK resources (educational CDs from an unspecified outside organization) encouraged him to “*demand the ultrasounds and everything*” and reinforced the perception that the “*pediatric community isn't really on top of it.*” While the majority of participants were highly educated and believed themselves to be capable of understanding technically complicated biomedical information, providers dissuaded a few participants from actively pursuing BEK, including one woman who recalled being told by her physician to “*step away from PubMed.*”

Against the backdrop of the perceived lack of information, patients struggled to quantify and interpret risk for specific phenotypes associated with their genetic result. Many participants felt that the resources they were able to accumulate should have been directly provided from clinicians and genetic counselors. Furthermore, the perceived lack of authoritative data available from independently derived BEK sources, such as the internet, became a deterrent for a handful of participants in seeking additional knowledge:

“I wasn't Googling and trying to dig for information because you don't know what you're looking for and you're just gonna upset yourself by finding out things that aren't necessarily true.”

When independently generated BEK did not alleviate emotional distress, resolve uncertainties, or provide more situational control, the knowledge *in toto* lost value. Some participants wished they did not have the information, transforming it into a kind of “toxic knowledge” (Bernhardt et al. 2013). As one prospective father recalled:

“We did a little bit of research online, but when you look online, you – it’s just nonsense. I mean some are true, some are false.”

Participants whose information needs were not met by BEK, and patients who did not arrive at a decision after receiving BEK, experienced feelings of frustration with the perceived lack of decisional support and biomedical direction that would allow them to pursue “next steps.”

Other Ways of Knowing

Participants utilized multiple sources outside the biomedical sphere to generate an expert knowledge base in the absence of biomedical certainty. This knowledge base is considered expert as, from a constructivist perspective, all knowledge is useful simply because it is being used, whether or not it is biomedically endorsed. The semi-structured interviews did not probe for specific “other ways of knowing,” so these findings originated organically through analysis.

Embodied knowledge. Some women referred to an instinctual, embodied knowledge regarding their pregnancy outcomes.

“I’m the pregnant one, when I feel it moving, I can feel it growing, I just feel like it’s going to be okay.”

This participant decided to terminate her pregnancy after receiving a pathogenic microarray result:

“Because of the physical abnormality... I had originally gone up, before I even had those results, to the [Hospital #1] in Manhattan. They said that it could be corrected, that there has been other cases. But, I don’t know, just something in my gut was, let it go.”

This “gut instinct” was a recurrent theme among our participants and a powerful way of knowing that increased decisional certainty, most noticeably for the two couples who terminated

the pregnancy. Various parts of the body became emotional loci and abstract physical representations of pregnancy decision-making:

“It was tough to realize that we were going to choose to abort the baby, but that's the decision we made and it was more of a gut feeling than just something in your heart that you knew that you needed to do.”

The “gut” informs the difficult decision of what “needs to be done” while the heart, signifying the idealized outcome of a normal pregnancy and promise of a healthy child, is overruled.

Spiritual beliefs. Religious teachings and beliefs exerted a strong influence on some participants who had been raised in religious or spiritual homes, or who drew personal identity from religious/spiritual sources.

One partner with a positive pathogenic result discussed the decision to continue the pregnancy with his genetic counselor:

“If you terminate now, how do you know honestly that our child would not have grown up healthy. We just don’t know. We just leave it up to Him up in the sky and hope for the best.”

Another patient used spiritual beliefs to reinforce her decision to terminate.

“I really believe that child picked that journey [...] to teach me and to just break me open. [...] But that's a very spiritual decision for me.”

Spiritual and religious beliefs validated decisions participants had already made but generally did not direct these decisions. In one case, a partner struggled to reconcile a pathogenic genetic result and possible abortion with the tenets of his religion.

“I'm Catholic and part of my main struggle was that it's abortion and it was against my religious upbringing, regardless of the condition. I've since changed my beliefs and core values on that, but going into that I felt 'doesn't this child deserve a chance?' And the fact

that the doctor- the second one- brought up examples of pastors he knows that's written books and essays and his stance was that it wasn't a sin. That gave me peace of mind."

In the excerpt above, the physician becomes the locus of the negotiation between BEK and other ways of knowing for the participant, citing related religious examples that permit abortion under certain medical circumstances. Through this, the partner is able to reconcile his religious values and the biomedical diagnosis in a way that strengthens the certainty of the decision to terminate the pregnancy.

Social network. Other sources of knowing came from interactions with family and friends who provided reassurance for pregnancy decisions. One patient's family emphasized the child would be "*loved the same way,*" regardless of any phenotypic abnormality. Another woman recalled her family's acceptance of a baby with potential disabilities after receipt of uncertain genetic results: "*We'll [the family] come help you more until you guys get adjusted. We'll take what comes and it'll be fine.*"

Participants leveraged knowledge from friendships when considering what a diagnosis of potential learning disabilities meant for their unborn baby:

"He [male partner] asked me "is there any physical deformities?" and I said "No, it's just mental—it's learning disabilities, it's possibly not meeting milestones" and he's like "Okay, so she'll be slow; who cares. Half of our friends are slow." And that's how we left it."

The experiences of other parents informed decisions based on perceptions of raising children with developmental disabilities and how this might impact quality of life for both the unborn child and affect parenting:

"We really had discussed all the possibilities and how we wanted to parent and we just don't have the means and the resources to care for a child...like my sister-in-law's friend caring for this child that has some serious medical needs—thank God they have the

resources for that...and we just don't and that was not something that we wanted to undertake.”

Though not formally sanctioned by clinicians, informal support groups through online organizations offered information for parents of children with rare chromosomal disorders. Websites, such as “Unique” and the social media platform Facebook, provided a space to share pregnancy experiences, gain social support for decision-making, and alleviate feelings of isolation in prospective parents. Referring to one such group, one woman recalled:

“You see pictures of their kids. Everyone's very friendly and they email each other and tell you what's going on. I still have these people asking me how the pregnancy's going because I told them I wasn't sure I was going to continue. [...] In the published reports there were eight pictures of kids and one of them looks severely mentally retarded and I was like ‘I'm out. I'm not gonna do that.’ Then you go on this Facebook page and most of these kids look pretty normal.”

By seeing pictures of children on Facebook with similar genetic diagnoses, this participant gained a measure of comfort that her own child will be phenotypically “normal,” which, alongside her statistical percentages for various medical outcomes given her unborn child’s genetic result, reinforced her decision to keep the pregnancy.

Family History: Bridging BEK and Other Ways of Knowing

Family medical history forms a natural bridge between BEK and other ways of knowing. Such knowledge is a composite of shared stories of health (usually) within families that trace their origins to, and gains biomedical legitimacy from, BEK. Health information from family history informed participants’ reasons to test, interpretation of results, and decisions to keep or terminate a pregnancy. Participants accrued this knowledge through oral histories of family medical conditions and health states and at the suggestion of providers while conducting additional genetic testing to help resolve uncertainty of genetic results. In considering a microarray result indicating risk for a nonspecific level of psychiatric illness, one patient

reflected:

“Psychosis runs in my husband’s family. So it’s pretty obvious to me that [the genetic disease] runs in the family, and so that also influenced my decision [to terminate the pregnancy], because I know what it looks like and it looks horrible. My husband’s aunt is actually locked up in a psychiatric hospital, unable to make sense of her world. She can’t even connect to another human being. So we’ve just seen so much evidence— I don’t know how to describe to you how clear our decision was. It wasn’t like “should” we terminate.”

Frequently, further genetic testing involved performing microarray tests on parents or other relatives indicated the variant was shared between one unborn child and at least one of the parents. A participant carrying multiples shared:

“It was still nerve wracking choosing to keep that boy because the doctor had said they thought it would be easier to keep the girl, even though it was abnormal, but it was abnormal like my husband.”

Participants gained greater decisional certainty following subsequent genetic testing of parents or relatives. When a parent or relative who did not display any cognitive or physical impairment also carried the variant, participants felt reassured that the variant would not prove deleterious. The expectation that the variant would phenotypically manifest the same way in the unborn child as it had in the adult might or might not be warranted, as this expectation was predicated on a statistical hedging of uncertain results. Only one participant noted that with variants of unknown effect size and phenotypic spectrums, “risk” to the baby remained hard to quantify, even if the parent presented as physiologically “normal.” This prospective mother noted, after being diagnosed with the same VUS as her unborn child,

“I’m the person who has it. That starts making you question like ‘Am I sane? Was I screwed up at all?’ But it seems to me that it’s a false sense of security if they’ve seen it in people [who] have this dramatic effect and then their parents—no effect. I’m tested; I’m ‘normal’ for whatever that means, or my development has been...however I don’t want to totally rely on that because I know that it could not have an effect on me and have an effect on my child.”

Family history thus became a “special case” in which participants used knowledge garnered from biomedical testing (including diagnoses of diseases, perception of disease risk, and results of genetic tests) to create and share narratives of health, inform interpretation of genetic results, and assist with making pregnancy decisions. Similar to the previous example of a partner utilizing spiritual beliefs that were supported by a physician to reach a decision, family history is another patient directed way of knowing that is informed by BEK derived resources. However, unlike independently pursuing BEK through the internet, which was a form of knowledge that had the potential to come from a biomedically validated base, family history was informed through both medical testing and oral histories of health and illness shared across generations.

DISCUSSION

In managing a pregnancy complicated by fetal genetic diagnoses, and before the pregnancy is considered by the state of residence as medically “viable,” women may elect to terminate a pregnancy. However, the ability of the bio-scientific community to interpret health implications of genetic variants remains far outpaced by the rate of their discovery, widening the therapeutic gap between what can be found versus what can be interpreted and treated (Cutting 2014). It is in this gap that CEK come to the fore as BEK reaches its limits. In this study, ambiguous prenatal microarray results precipitated a crisis in which participants harnessed multiple knowledge platforms including biological expert knowledge and “other ways of knowing.” These ways of knowing will be increasingly critical as genetic testing, such as genome and exome sequencing, yield novel results with uncertain implications. When

biomedical experts cannot provide prospective parents with the information they require to make pregnancy decisions, prospective parents will likely seek other types of experts and expert information.

Cultural Expert Knowledge

A growing body of research evaluates the way that patient-accumulated knowledge is assembled through direct sensory experiences (sometimes called embodied experiential knowledge) and through the experiences of others (or empathic experiential knowledge) (Abel and Browner 1998; Borkman 1979; Etchegary et al. 2008; Lippman 1999) to augment medical interpretations and/or to facilitate decision making (Downing 2005; Hallowell 2006; Parsons and Asch 1992). In its present definition, experiential knowledge is often assumed to be a subjective knowledge of the self and body (Abel and Browner 1998; Boardman 2011) or a suite of religious and spiritual beliefs (Cadge and Bergey 2013). Using this definition, “experiential” knowledge failed to capture the full breadth of informational sources that participants draw from outside the biomedical expert framework. Rather, we found that experiential knowledge was informed by complex systems of social networks and religious/spiritual beliefs.

Experiential medical knowledge is frequently juxtaposed against scientific and/or biomedical categories of “expert” knowledge, where all knowledge outside the “expert” system becomes “non-expert.” The false dichotomization created with the terms BEK and non-expert knowledge delegitimizes other lay forms of knowledge that patients utilize to understand ambiguous medical results and make decisions. Alternate platforms of knowledge may provide patients with powerful supports for decision making, particularly when medical results are uncertain and BEK can offer no further insights. Neglect of “other ways of knowing” in

biomedical and scientific discourses and clinical practice does a disservice to patients wishing to make an informed decision.

To encompass the multiple sources of information that patients draw from outside of biomedical knowledge, and to create a more inclusive and holistic understanding of knowledge types, we offer here that “other ways of knowing,” as interpolated from this research, may be more succinctly defined as “Cultural Expert Knowledge”, or CEK. CEK is defined as non-expert public domain or “collective” public knowledge, advice derived from experienced family, friends, and other social supports, religious/spiritual beliefs and practices, and metaphorical knowledge (including embodied knowledge and knowledge from previous pregnancies or shared pregnancy narratives). BEK relies on empirically legitimated medical information traditionally disseminated from clinicians to patients (Jordan 1997) and is structured in ways that focus on objective facts and omit subjective experiences (Holmes and Ponte 2011). CEK allows participants to generate knowledge in discourse with others beyond the biomedical encounter. This allows patients to take ownership of their bodies, question (the absence of) biomedical knowledge, and facilitate the creation and dissemination of pregnancy narratives, subjective opinions, and engagement in religious and spiritual practices.

Significantly, in multiple instances CEK provided the only source of information for some participants. Interactively shared stories and experiences between parents of children with variants identical to those identified in the fetuses of our participants frequently became the most empirically valid knowledge available. Such lay expertise helped participants conceptualize the potential experience of parenting a child with disabilities linked to a pathogenic genetic variant or a VUS.

Implications for research and practice

Conceptions of what makes a fully informed health-literate patient vary. The Institute of Medicine implements a nuanced definition of “health literacy” that includes “cultural and conceptual knowledge,” or family, social, and cultural influences shaping beliefs and attitudes about health (Health Literacy: A Prescription to End Confusion 2004). Research exploring the effect of health literacy and numeracy on patient responses to receipt of information about personal genetic risk for hereditary disorders and genomic susceptibility to complex diseases is limited (Lea et al. 2011). Despite this, the field of public health genomics has increasingly focused on methods to advance genomic health literacy to empower patients in making informed and values-based health decisions (Johnson et al. 2005; Syurina et al. 2011). In efforts to narrow the information gap among pregnancy stakeholders faced with uncertain genetic results, consideration of what constitutes their cultural and conceptual knowledge base is warranted. The present research demonstrates how CEK can complement BEK. Participants were versatile in their use of multiple knowledge platforms. This increased their total knowledge informed decision making.

However, CEK is by its person-specific nature hard to empirically quantify and utilize in biomedical settings. Contextual and personal factors, such as sociodemographic characteristics and psychosocial variables (goals, beliefs, values, attitudes, emotions, personality traits), influence whether someone with informational needs in BEK and CEK will actually seek information (Allen 1996; Case et al. 2005; Czaja, Manfredi, and Price 2003; Lambert and Loiselle 2007; Loiselle 2001; Loiselle and Delvigne-Jean 1998; Shiloh, Sinai, and Keinan 1999). One system of CEK cannot be extrapolated into another context without reevaluation of the research participants, subject content, and environment. One limitation of this study is that it is based on a predominantly white, well-educated, heterosexual population with religious

affiliations (or lack thereof) that do not match national trends (America's Changing Religious Landscape 2015). This particular sample may have been uniquely driven to accrue diverse types of available information, and thus this finding that may not replicate in larger, more heterogeneous populations. While outcomes may not be the same across other demographics, many participants evidenced strong desires to pursue additional BEK sources beyond their own clinician as a way to gain control over a situation with an unknown or speculative outcome. Many also sought other lines of evidence beyond the biomedical to inform decision making.

Future clinical and genetic counseling work in this area may benefit from thoroughly assessing patient and partner informational needs prior to the start of prenatal genetic testing. This could include sensitive discussions specific to patients and their partners regarding health literacy, networks of values and beliefs, social networks, and family history (Werner-Lin, McCoyd, and Bernhardt 2016). Given the myriad constraints on clinician resources (including time and market availability of medical experts), we recognize that it will be difficult to operationalize counseling that incorporates CEK in the counseling/clinical moment. However, this does not preclude participants from being directed to medical literature, links for support groups (online and in-person), and reputable websites. These resources could be distributed as a handout or email, and indeed, the participants in this study desired these types of specific informational resources. This expressed interest may warrant the development of materials and methods to make them available. Expanding the array of information available to patients and their partners may assuage distress in the face of uncertainty. In the case of results with uncertain or variable outcomes, CEK may be the only available form of information for patients and their partners to utilize. The recognition of CEK as a legitimate source of expert knowledge by biomedical personnel can buoy participant's decisional confidence. This support can facilitate

participants' integration of total knowledge, including locally specific values and beliefs, to make the most maximally informed decisions possible.

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Table 1: Participant Demographics

	Female patients (N = 27)		Male partners (N = 12)	
	N	%	N	%
Age				
20–30	5	18.5	0	0.0
31–40	18	66.7	11	91.7
41+	4	14.8	1	8.3
Education				
Less than a Bachelor's degree	3	11.1	1	8.3
Bachelor's degree	12	44.4	5	41.7
Master's degree	7	25.9	3	25.0
Professional or Doctoral degree	5	18.5	3	25.0
Religious affiliation				
Catholic	4	14.8	6	50.0
Jewish	6	22.2	2	16.7
Protestant	3	11.1	0	0
None	12	44.4	1	8.3
Other	2	7.4	2	16.7
N/A	0	0.0	1	8.3
Self-identified ethnicity				
Asian	3	11.1	0	0
Asian/white	1	3.7	0	0.0
Black	1	3.7	0	0.0
White ^a	22	81.5	11	91.7
N/A	0	0.0	1	8.3

	Female patients (N = 27)		Male partners (N = 12)	
	N	%	N	%
Works in health profession	6	22.2	1	8.3
Has biological children	14	51.9	6	50.0
Married/partnered	24	88.9	120	100.0

Table 2: Codes and Definitions

Term	Definition
Amniocentesis	Prenatal test that samples fluid from the amniotic sac surrounding a developing fetus to obtain genetic information.
Chorionic Villus Sampling	Prenatal test where a sample of the placenta villi is taken through the cervix or abdominal wall to obtain genetic information about the developing fetus.
Chromosomal Microarray	Clinical genetic test that evaluates genomic copy number through microarray technology (includes array-based comparative genomic hybridization, or a CGH, and single nucleotide polymorphism, or SNP, arrays).
Copy Number Variant (CNV)	A type of structural genomic variation characterized by insertions, deletions, and/or duplications of genomic material that vary between individuals. CNVs can be beneficial, harmful, or neutral depending on the specific variant that is lost or gained.
<i>De novo</i> variants	Novel genetic variants found in a germ cell (egg/sperm) or fertilized egg (zygote) that are not inherited from either parent.
Karyotype	An individual's collection of chromosomes, which can be visualized via laboratory image to reveal abnormalities (i.e., more or fewer chromosomes than the normal 23 pairs, abnormally truncated chromosome arms, etc.).
Phenotype	Observable traits in an individual such as height, blood pressure, IQ, muscle tone or dysmorphic features. The genetic contribution to a phenotype is referred to as the genotype.
Placental mosaicism	This occurs when a discrepancy is found in the number of chromosomes in a placental cell versus the number of chromosomes present in a fetal cell; e.g., a trisomic cell could be found in a placental biopsy, but the developing fetus possesses a normal diploid chromosome complement.
Variant of Uncertain Significance (VUS)	A genetic variant of unknown implications for which insufficient evidence is available to make an unequivocal determination of clinical significance. VUS results can be divided into variants that are likely pathogenic, likely benign, or unknown. Additional research and testing are often indicated after receipt of a VUS result.

Table 3: Table Prenatal Microarray Results

Pregnancy	Lab classification of copy-number variants	Inheritance of copy-number variants	Expected Phenotype Associations	Pregnancy outcome
313	Pathogenic	Unknown	Autism, seizures, Tourette's Syndrome	Continuing
202	Pathogenic	<i>De novo</i>	Neurocognitive defects, dysmorphic features, heart defects	Terminated
201	Pathogenic	<i>De novo</i>	Neurocognitive defects, cardiac abnormalities, immune deficiencies, psychiatric issues	Terminated
306	Likely pathogenic	<i>De novo</i>	Extremely variable, Normal IQ to learning disabilities	Continuing
315	Uncertain	Inherited	Variable expressivity; Normal development to intellectual disabilities, autism, seizures, psychiatric illness, motor delay	Continuing
304*	Uncertain/ Uncertain	Inherited / <i>De novo</i>	Not known to be associated with a specific phenotype (both variants)	Continuing
301*	Uncertain/ Uncertain	Inherited / Inherited	Possible risk for periventricular heterotopia//Not known to be associated with a specific phenotype	Continuing
101*	Uncertain/ Uncertain	Inherited/ Inherited	Increased risk of autism, learning disabilities, abnormal behavior, motor delays	Continuing
319	Uncertain	Unknown	Not known to be associated with a specific phenotype	Continuing
318	Uncertain	<i>De novo</i>	Variable expressivity; Normal to intellectual disabilities, ADHD, autism, seizures, psychiatric illness, hypotonia	Continuing
309	Uncertain	Unknown	Possible association with X-linked mental retardation	Continuing
308	Uncertain	Unknown	Intellectual disability, seizures, abnormal behavior	Continuing
303	Uncertain	Inherited	Not known to be associated with a specific phenotype	Continuing
109	Uncertain	Unknown	Variable penetrance; Increased risk of neurocognitive deficits, schizophrenia, microcephaly, congenital cardiac defects	Continuing
108	Uncertain	Unknown	Variable penetrance; Developmental delay, mental retardation, learning disabilities, autism, ADHD, abnormal behavior	Continuing
103	Uncertain	Inherited	Variable expressivity. Normal IQ to mild retardation seen.	Continuing
310	Likely benign	Inherited	Kabuki-like syndrome	Continuing
312	Likely benign	Inherited	Not known to be associated with a specific phenotype	Continuing
302	Likely benign	Unknown	Not known to be associated with a specific phenotype	Continuing
300	Likely benign	Inherited	Not known to be associated with a specific phenotype	Continuing
111	Likely benign	Inherited	Not known to be associated with a specific phenotype	Continuing
106	Likely benign	Inherited	Possible increased risk for schizophrenia	Continuing
105	Likely benign	Inherited	Possible increased risk for cystic renal disease	Continuing
104	Likely benign	Inherited	Not known to be associated with a specific phenotype	Continuing
107**	Likely benign	Inherited	Not known to be associated with a specific phenotype	Selective reduction of twin A
307	Not available	<i>De novo</i>	Unavailable	Continuing
112**	Not available	<i>De novo</i>	Variable phenotype associated with overgrowth syndrome and risk for tumor development	Continuing

*- Two CNVs identified

**- Carrying multiples