I, Sarah Adelsperger, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Parental Reasons and Reactions toward Return of CYP2D6 Research Results and Perceived Benefits and Harms toward Hypothetical Incidental Findings

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Parental Reasons and Reactions toward Return of CYP2D6 Research Results and Perceived Benefits and Harms toward Hypothetical Incidental Findings

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Abstract

Background: CYP2D6 contributes to the metabolism of more than 25% of drugs prescribed in a clinical setting. Pharmacogenetic testing for CYP2D6 can be beneficial by informing drug selection and dosing. Return of CYP2D6 research results provides the opportunity for direct benefits not typically available to research participants. Knowledge about parental reasons for participation and reactions to return of CYP2D6 pharmacogenetic testing could inform research practice. Genomic studies including those that use genomic approaches for drug response studies also hold the potential to produce incidental findings, but no consensus exists around which incidental findings to report back to children and parents. The purpose of this study was to assess parental reasons for participating in research involving the return of their child’s CYP2D6 research results, and reactions to the receipt of results. This study also explored parents’ perceptions of the benefits and harms of hypothetical incidental findings.

Methods: We conducted qualitative interviews with 61 parents following the return of CYP2D6 pharmacogenetic research results. Interview questions probed their reasons for participating, reactions to the results, and the benefits and harms they perceived in the return of incidental findings. All interviews were recorded and transcribed verbatim. Transcripts were coded and analyzed for major themes and subthemes.

Results: Thirty-one parents of children who were naïve to opioids and 30 parents of children who were previously exposed to opioids participated in the qualitative interviews. No major topical differences were seen between the two groups. The most common reasons given for participating in the study were to help their child and to learn information pertinent to health generally. Less frequently provided reasons included helping others, contributing to research,
and trusting CCHMC. When asked about reactions to their child’s CYP2D6 research results, parental responses reflected two broad themes: “perceived normality” and “emotional appraisal filtered through expectations.” Perceived normality included perceptions that “the child is medically normal” or “the child is socio-culturally normal.” Parents also discussed “enabling proactive responses to potential health threats” in regards to benefits of hypothetical incidental findings, and discussed “harm to the parent's mental or emotional well-being” in regards to harms of hypothetical incidental findings.

**Conclusions:** Our findings related to reasons for participation are consistent with previous genomic studies. Our findings suggest that parents are willing to have their children participate in pharmacogenetic research if they view it as beneficial for child or themselves. Themes related to reactions to the results suggest that pharmacogenetic results will not affect parental interactions with child. Parents felt that if they were presented with incidental findings, that the benefits would be that they would be able to improve decisions related to health, and/or advocate for themselves or their child. In regards to harms, parents discussed stress or anxiety as the most likely harm that came from the hypothetical return of incidental findings.
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Introduction

CYP2D6, a member of the superfamily of cytochrome P450 enzymes, contributes to the metabolism of more than 25% of drugs that are prescribed in a clinical setting, such as opioids (like codeine) (Leppert, 2011; Samer, Lorenzini, Rollason, Daali, & Desmeules, 2013). Codeine is an analgesic drug that is often administered within the pediatric population to manage pain post-surgery because of a lower incidence of side-effects (Prows et al., 2013; Williams, Patel, & Howard, 2002). Codeine is O-demethylated into morphine through CYP2D6 (Kirchheiner et al., 2007; Thorn, Klein, & Altman, 2009). There are more than 80 variants of CYP2D6 that contribute to a variety of metabolic phenotypes related to codeine metabolism (Leppert, 2011).

Pharmacogenetic testing is available for CYP2D6, and the results from pharmacogenetic tests can assist in improving drug response and treatment efficacy by informing drug selection/dosing processes (Crews et al., 2014; Relling & Klein, 2011; Wang, McLeod, & Weinshilboum, 2011).

The American Academy of Pediatrics (AAP) recommends that if pharmacogenetic testing is indicated in children, it is acceptable to complete with parental permission and, when appropriate, the child’s assent. Additionally, the AAP recommends that if the pharmacogenetic test may produce information with implications beyond drug response such as diagnostic or prognostic implications, that these implications must be discussed before testing is undertaken (Ross, Saal, David, & Anderson, 2013). Although detailed statements by the AAP have been made in terms of recommendations for diagnostic testing, newborn testing, carrier testing, predictive testing, histocompatibility testing, and direct-to-consumer testing, few recommendations have been made about pediatric pharmacogenetic testing. Knowledge about parental understanding of and expectations for return of CYP2D6 pharmacogenetic testing could inform research and clinical practice.
Genomic studies including those that use genomic approaches for drug response studies hold the potential to produce incidental findings, or information that was not being sought as part of the study’s aims yet has potential health or reproductive significance. No consensus exists around which incidental findings to report back to children and parents. Due to the nature of pediatric consent, parents are able to learn about incidental findings about their children. Because both parents and children are involved in the return of results, ethical dilemmas can occur when one party wants result information, and the other does not (Avard, Senecal, Madadi, & Sinnett, 2011). Further dilemma could arise if parents wish to receive their child’s results about adult-onset and untreatable conditions. Several studies suggest that a large majority of parents wish to receive results for untreatable fatal conditions and adult-onset conditions (Fernandez et al., 2014; Kleiderman et al., 2014; Tercyak et al., 2011).

The purpose of this study was to assess parental reasons for participating in research involving the return of their child’s CYP2D6 research results, and reactions to the receipt of results. This study also explored parents’ perceptions of the benefits and harms of hypothetical incidental findings.
Methods

Participants

The participants of the larger mixed methods eMERGE study at Cincinnati Children’s Hospital Medical Center (CCHMC) consisted of parents whose children (half naïve to opioids and half previously exposed to opioids) were previously enrolled in one of three protocols in which stored DNA was accessible for further research. The previous studies were Personalizing Perioperative Morphine Analgesia in Children (PPMA), Cincinnati Genomic Control Cohort (GCC), and Better Outcomes for Children (BOFC).

Study invitation letters were mailed to the parents of children enrolled in PPMA, GCC, and a random sample of those from the BOFC who met criteria for this study. Parents who were uncertain of their child’s opioid exposure status were excluded. Cases for the larger study were parents of children younger than 18 years old who had a history of exposure to a prescribed opioid. Controls were parents of children younger than 18 years and naïve to prescribed opioid drugs.

For the larger study, a study coordinator mailed invitation letters to parents of children enrolled in PPMA and GCC. A study coordinator involved in BOFC mailed invitation letters to parents of children in BOFC. The letter included brief information about the workings of the study and contact information for the study coordinator if parents were interested in participating. If GCC participants did not contact the study coordinator after a month, the study coordinator followed-up by telephone to assess interest in the study. If BOFC participants did not contact the BOFC coordinator, the BOFC staff sent a second letter inviting them to the study initially, although this did not occur for the majority of the study.
If parents were interested in the study, the study coordinator mailed or e-mailed copies of the consent form and questionnaire. Then the study coordinator set up a telephone appointment to go through informed consent. By mailing/e-mailing the consent forms ahead of time, this allowed the parents to have the consent form in front of them during the telephone appointment. After verbal consent was given by parents, they were asked to mail/e-mail their signed and dated consent form to the study coordinator. If GCC parents did not respond to the initial mailed invitation, the study coordinator contacted them via phone to gauge interest and then provided verbal details about the study. If verbal consent was given during the phone call, parents were mailed/e-mailed the consent form so that it could be signed, dated, and mailed/e-mailed back.

Parents who returned appropriately signed consent forms were considered enrolled participants. Parents were considered screened but not enrolled participants if the signed consent form was not received. In this event, no related study procedures occurred and the parent was not re-contacted. When parents inquired about the study, the coordinator asked parents about their child's prescribed opioid history to either confirm (for PPMA participants) or establish (for GCC and BOFC participants) their child's opioid exposure status. GCC and BOFC participants were then placed in either the case or control group, based on their responses.

After participants' children’s stored DNA samples were genotyped for CYP2D6, results were disclosed by phone at a pre-arranged appointment. Parents were also told that following the return of their child’s result that they would be asked to complete a telephone questionnaire. Following completion of the telephone questionnaire, participants were mailed a $10 incentive.

A subset of participants in the larger study was asked to participate in a qualitative telephone interview to gain an in-depth understanding of parents’ reactions to their child’s results. Half of these participants had children who were naïve to opioid (controls), and half had
children who were previously exposed to opioids (cases). The qualitative interview occurred within 2 weeks of the returned results and quantitative survey. Participants were also provided with a $10 incentive after completion of the interview. In this manuscript we report the findings from the qualitative portion of our mixed methods study.

*CYP2D6 Pharmacogenetic Test/ Results Disclosure*

Participants’ children either previously underwent *CYP2D6* testing (for PPMA participants) or had *CYP2D6* testing conducted on their stored samples after consent (for GCC and BOFC participants). All samples had the same *CYP2D6* assay conducted in the CLIA-approved and CAP-accredited CCHMC Molecular Genetics Laboratory. The laboratory returned genotypes in “* allele” nomenclature to a research team member (CP) who interpreted the genotypes to assign predicted phenotypes and then returned the results to participants. Result specific scripts were used to assure consistency in result messaging (Table 1).

*Data Collection*

The interview guide questions for the qualitative interviews aimed to produce a deeper understanding of the reasons, expectations, and perceptions that shaped parents’ participation and attitudes towards their child’s research results (Appendix 1). Questions were open-ended. Three interviewers were trained to conduct interviews using the qualitative interview guide and encouraged to use impromptu probes to elicit participant elaboration on the issues discussed. Interviewers underwent training including practice interview sessions over a two week period prior to interviewing participants. Interviews were audio recorded. The recordings were transcribed verbatim, and the transcript was then compared to the recording to verify accuracy.

Questions from the interview guide (Appendix 1) that inform this manuscript include:

1) Why did you decide to participate in this study?
2) How did today’s information compare to what you were expecting to learn? ;

3) How are you feeling after learning about your child’s results? ;

4) From your perspective, what do your child’s results mean for your child? ;

5) How will the results affect your interactions with your child? ;

6) What do you believe could be the benefits of learning incidental finding results from genetic research studies? ;

7) What do you believe could be the harms of learning incidental results from genetic research studies?

Data Analysis

Codes were initially identified both inductively based on a reading of 55% of the transcripts and deductively based on issues raised in the literature or by members of the research team. Additional themes were added as new issues were identified in additional interview transcripts. Coding was conducted using ATLAS.ti (Version 7.5, ATLAS.ti Scientific Software Development GmbH) by two coders (SA & JL). Coders were trained to apply codes according to the code guidebook (Appendix 2).

Inter-rater reliability was established after both coders coded the first thirteen transcripts, and the first thirteen transcripts were used to calculate Cohen’s kappa in which a 0.60 cut-off for agreement was used. After inter-rater reliability was established, coding was reviewed by the second coder (JL) every 5 transcripts to maintain continued inter-rater reliability. Cohen’s kappa was determined to be 0.670 for Reasons for Participating, 0.660 for Reactions to Results, 0.773 for Perceived Benefits of Hypothetical Incidental Findings, and 0.741 for Perceived Harms of Hypothetical Incidental Findings, which all indicated substantial inter-rater reliability.
Coding was then analyzed to identify any themes that cut across the coding categories. Themes were identified and confirmed using researcher triangulation (Denzin, 1970) where members of the research team individually identified potential themes and the final themes were determined by consensus.
Results

Sample Characteristics

Our sample was composed of 31 parents of children who were naïve to opioids and 30 parents of children who were previously exposed to opioids. No major differences were seen between case and control groups. The majority of participants were mothers (n=59), of whom two identified as “adopted mother.” The majority of participants identified solely as white or Caucasian (n=56). Only 5 parents in the cases group self-reported as non-White / non-Caucasian (Table 2).

Almost two-third of the parents in this study were either 4-year college graduates (n=28) or had more than a four year college degree (n=10). Over half of parents reported a total household income of more than $74,999 (n=33). All parents of the study had health insurance of some type, and all children involved with the study had health insurance except one child. Almost half of the parents involved in this study identified with working in healthcare, healthcare related industry, or in biomedical research in the past (n=30), and of the total study population, 19 individuals were not employed at the time of the study.

Reasons for Participating

Interview transcripts were examined for reasons why participants agreed to participate in the study and to receive their child’s pharmacogenetic research results. Table 3 lists codes used to describe parents’ reported reasons for agreeing to participate in the study and why they chose to receive their child’s pharmacogenetic research results. Learning about health was the most common reason for participation in the study (n=35). For example, one parent said, “I just think it’s a better awareness of his health. He has to acknowledge that anything he takes, even if he thinks he’s got a headache, that everything interferes with your body. It’s all chemicals, and changes happen, and he should be aware at an early age if he has to be concerned about
somethin’ or not, and no matter what he drinks or eats or medication, it all has somethin’ to do with his body.” Helping their child was identified as a reason for participation by over half of the participants (n=32) and parents discussed that the information they received will help them make medical/health decisions for their child. For example, one parent stated, “You never know, especially with medications and such, there’s always new treatments and everything coming out through the course of his life that something we had done, say, to see his genetic makeup that could possibly make a difference in his future treatment.”

Fifteen parents discussed contributing to research as a reason for why they participated in this study, and eleven parents identified helping others as a reason. One parent stated that, “Anything that would research into why people react the way they do is valuable.” Seven parents discussed trusting CCHMC as a reason for participation, and these participants discussed that they participated specifically because of CCHMC whether it was because of their clinical care or research profile.

Reactions to Results

Interview transcripts were also examined for participants’ reactions to the return of the CYP2D6 research result. Table 4 lists codes that describe parents’ reactions toward the return of the CYP2D6 research result. Two themes emerged from the coding: “perceived normality” and “emotional appraisal filtered through expectations.” Perceived normality was characterized as either “the child is medically normal” or “the child is socio-culturally normal”.

“The child is medically normal” reflect parents’ responses that the child's treatment for pain does not require changes in medication as a result of the CYP2D6 pharmacogenetic test results. One parent, when asked to describe their understanding of the results, said, “That he would be OK to get a normal dose of pain medication, that he should react the way the medicine
is meant to react.” Another parent said, “From what I understood of the way it was explained to me … he can take pain medication and it’s not going to affect anything.” When discussing medicine and their child's results, parents focused on whether drug doses or treatment were “normal.” Only one parent mentioned the genetics result being “normal.”

“The child is socio-culturally normal” characterized responses to questions about the meaning of the results for the child and influence of the results on parent-child interactions. This captures almost all the specific questions and probes except for the influence on health. For example, one parent stated, “I’m not gonna look at him any different because he can’t take codeine.” Another parent said “I don’t think she would view herself as any different than any other kid just because her body doesn’t process a drug the same way. It’s not visible per se.” Another parent said “I feel fine. I’m glad to know ‘em, but they’re not gonna change the way I do anything.” Of note, the majority of remarks coded under changes nothing (132/153) fit into the second theme of “the child is socio-culturally normal” meaning that the results will not change how they view their child or how their child views his- or herself.

The remaining codes informed the theme, “emotional appraisal filtered by expectations” which means that parents’ reactions were shaped by the expectations with which they entered when they consented to participate in this study. Parents commonly had no prior expectations regarding the receipt of their child’s CYP2D6 research results (n=40). For example, one parent stated, “I don’t know that I had any true expectations. I wanted to learn as much as possible, and when they said that they were gonna do a gene study to find out how ___ might react to some medicines, I was interested in finding out what the results of that might be so we don’t give him medicines that aren’t effective, things that aren’t gonna work. I didn’t really have any expectations, because I didn’t know what to think about it.” Because the return of
pharmacogenetic results was outside of their experiences, participants whose responses fit this code did not have any strong, prior expectations. Far fewer (n=6) described the result as expected/unsurprising. For example, one parent said “I think it was pretty much what I expected to learn. I think I kind of understood what they were looking for when they were doing the research, and I had seen the way my son responded with the medication they had given him. So I pretty much wasn’t surprised when she told me that they found that that works well for my son.” For parents like this one, their child’s previous experience with pain medication predisposed the parents to expect a certain type of result, which they in fact received. Out of the six parents who were not surprised by their child’s CYP2D6 results, three children had extensive metabolizer status, one child had extensive metabolizer (2A-2A) status, and the other two children had intermediate metabolizer status. Eight parents expressed surprise toward their child’s research result in terms of how much more information or detailed information they learned at the return of results than they were expecting to learn. One parent said, “I wasn’t expecting anything, and the fact that they had specific details about my child and what her body can handle and what it couldn’t was kind of a surprise.” Twenty parents expressed that the information was interesting, and two parents expressed worry toward the research result in terms of extra information that they might learn about their child. One parent said “I was a little concerned, because I really wasn’t sure—I mean, I knew it had something to do about pain management, but I wasn’t sure what exactly, and I was a little, like, leery, like, ‘What if I learn something really bad?’” Three parents expressed that they wanted to seek information in addition to the results they received. Two of those three parents who expressed wanting additional information discussed wanting to seek additional information about their child’s risk for disease and the other parent discussed wanting further information to give to the child’s physician. In terms of wanting information
about the child’s risk for disease, one parent said, “I was interested in finding out about different diseases, if he would be at risk for anything, either now as a childhood disease or further on down the road as an adult.” The parent who discussed wanting further information for the child’s physician said they wanted to seek “More information that I could give a pediatrician or something down the line if he were to require pain medication.”

*Perceived Benefits of Hypothetical Incidental Findings*

An additional focus of the interviews was parental perceptions of the benefits and harms of possibly receiving incidental research findings for their child and/or themselves. Table 5 lists codes that describe parents’ perceived benefits of receiving hypothetical incidental findings. Cutting across parents' responses to the question was a theme of “enabling proactive responses to potential health threats.”

Many parents (n=52) discussed that the information itself or the opportunity to receive it would be beneficial. For example, one parent stated “Knowing what could be coming, whether it’s treatable or untreatable at that particular moment in time, is going to be a benefit to the parents and to the child’s pediatrician, potentially, so that you can be on the lookout for symptoms and catch those much earlier than maybe you would otherwise.”

A benefit for the child and/or the parents that was identified by eleven parents was making better decisions. One parent described the benefit of incidental findings as “In some instances, it would give you choices about what to do and even if there isn’t anything you could do, you would at least be sort of forewarned.” Two parents discussed the ability to advocate for the child and/or themselves in future medical encounters.
Perceived Harms of Hypothetical Incidental Findings

A range of potential harms of receiving incidental findings were considered by parents. Table 6 lists codes that describe parents’ perceived harms of receiving hypothetical incidental findings. The harms reported are thematized as “harm to the parent’s mental or emotional well-being” related to the child and/or their own incidental findings. The one exception to this theme was concern about insurance.

Almost three-fourths of parents identified stress or anxiety as a potential harm (n=45). One parent described the harm related to incidental findings as “The worry, the fear, if you let if take over your life, if you’re one of those types of individuals who will sit there and dwell on the negative, as opposed to figuring out how to handle it.” Eight parents expressed that there could be unmeasured and/or unanticipated factors. Many parents discussed other factors contributing to risk besides the genetic factors such as environmental or lifestyle factors, or having genetic risk factors that aren’t fully penetrant. For example, one parent said, “You might think that you could get a disease and you could think that you’re gonna get it through your whole life and never get it.” Additionally, six parents expressed receiving results related to having an untreatable disease as a harm. For example, one parent stated that “If it were something that’s untreatable and uncurable and maybe is happening later on in life, I don’t think that I would like to know that. I think it would be too much information and I would worry about it all the time.” Finally, four parents were concerned that a positive hypothetical incidental finding could impact the family or child’s ability to get some type of insurance in the future.
Discussion

Overall, almost twice as many parents discussed reasons for participating related to helping their child or learning about their child’s health when compared to more altruistic reasons such as contributing to medical research or helping others. This suggests that in research that could provide a direct benefit for participants, like pharmacogenetic research, parents are willing to have their children participate if they view it as beneficial for the child or themselves. This is consistent with previous studies that have found that parents consent to genomic research for reasons related to helping their child or learning about their child’s health (Burstein, Robinson, Hilsenbeck, McGuire, & Lau, 2014; Harris et al., 2012).

When asked about what the results mean for the child, or how the results will affect interactions with the child, some participants answered with responses related to “the child is medically normal” and others responded with answers related to “the child is socio-culturally normal.” One parent mentioned the genetics result being “normal.” Within CYP2D6 pharmacogenetic testing, many parents interpreted (or understood) their child as normal if the test results indicated no change in how the child would receive medication or indicated no increased risk of side effects. The overall focus on treatment might reflect how the results were returned by the APRN. Parents emphasized that test results would not alter their behavior toward their child or their child’s attitudes toward themselves. Many parents conveyed that the results changed nothing or described their child as “fine” regardless of the specific CYP2D6 pharmacogenetic result their child received. Given concerns about “genetic essentialism,” or the belief that genetics influences one’s identity (Dar-Nimrod & Heine, 2011; Nelkin & Lindee, 1995; Parrott, Kahl, Ndiaye, & Traeder, 2012), these results suggest that parents do not regard a child differently based on CYP2D6 research results. This contrasts with previous studies that have
shown that when parents receive positive genetic testing results related to disease predisposition or genetic testing results that show an actual disease is present, parents have more anxiety and show more concern for their child (Grosfeld, Beemer, Lips, Hendriks, & ten Kroode, 2000; Lalatta et al., 2010). It should be noted however, that there are significant differences between research pharmacogenetic testing for CYP2D6 and clinical predisposition or diagnostic testing. Clinical predisposition and diagnostic testing has the potential to provide more life-altering information, such as life expectancy or what to expect from the natural history of a disease. Pharmacogenetic research results may inform drug selection or dosing for participants. Although these types of predisposition testing are different, they are similar in that they are both providing information to parents regarding their child’s health information.

Reactions to hypothetical incidental findings framed both benefits and harms as focused on the child and/or the parent. In response to hypothetical incidental findings, parents’ responses thematically emphasized the perceived benefit of incidental findings as their capacity to enable the parent’s proactive response to potential health threats. Parents felt that if they were presented with incidental findings, that the information itself would be good, that they would be able to improve decisions related to health, and/or advocate for themselves or their child. Many parents discussed that they felt that even if they learned about something that was untreatable in relation to themselves and/or their child, it would still be helpful information so that they could prepare for it. In terms of perceived harms of hypothetical incidental findings, responses thematically emphasized that the perceived harms were “harm to the parent’s mental or emotional well-being”. Parents discussed stress or anxiety as the most likely harm that came from the hypothetical return of incidental findings in stark contrast to the CYP2D6 results they actually received. They also discussed how there could be unmeasured and/or anticipated factors which
could misconstrue their perception of risk. This could mislead parents by implying an unwarranted genetic determinism especially when discussing multifactorial disease, and ignoring environmental and lifestyle risk factors. The exception to this theme of “harm to parent’s mental or emotional well-being” was the topic of insurance. Four parents discussed that they had concerns about how insurance companies might view or use the information from an incidental finding to the detriment of themselves or their child. Parents discussed “insurance” generically, except for one parent who identified life insurance, so it is not clear what types of insurance coverage were meant. It is possible that parents feared an impact on their child’s ability to get health insurance, despite the 2008 Genetic Information Non-Discrimination Act (GINA). A recent study by Fernandez et al has shown that with regard to hypothetical incidental findings, parents are concerned about their own and/or child’s ability to receive health insurance in the future. Although ability to receive insurance was a concern, parents still showed great interest in receiving incidental findings (Burstein et al., 2014; Fernandez et al., 2014). Other studies have also found that even when incidental findings and/or secondary findings are a possibility within genetic testing for children, parents show great interest in receiving those results even when other concerns are presented (Bergner et al., 2014; Levenseller et al., 2014; Sapp et al., 2014; Shahmirzadi et al., 2014). Future research could examine what types of insurance parents mean, and if health insurance is identified as a concern, then future public outreach should reaffirm the protections provided by GINA.

Beyond the limitations inherent to qualitative methods, such as small sample size or the researcher’s presence during data collection which has the potential to influence participant response (Anderson, 2010), there were other limitations within our study. One limitation of this study was the demographic homogeneity of the research participants. Participants were
predominately well-educated white mothers from households with incomes well above the national average. Additionally, almost half of the participants previously worked in healthcare, a healthcare-related industry, or in biomedical research. Participants’ work experience could influence their knowledge and attitudes about pharmacogenetic testing. Also, participants’ education and income might allow them to examine information related to the pharmacogenetic results because of access to resources, thus reducing any anxiety produced by test results and minimizing attitudes or beliefs, like genetic essentialism, that could be detrimental to empowering, effective health decisions on behalf of their child. Although access to resources could reduce anxiety for pharmacogenetic results, some parents still expressed concerns such as anxiety for some types of hypothetical incidental findings.

Future studies should try to expand the racial, gender, educational, and socio-economic diversity of the research participants. Future studies could also examine claims about the child’s medical or social normalcy to identify any interaction or overlaps between the claims and how they might impact the reception of future genetic and pharmacogenetic results. Finally, as noted earlier, parental concerns about insurance should be examined further, especially with a more diverse sample whose access to health insurance might be limited, to see how those concerns are discussed.
<table>
<thead>
<tr>
<th>Template Used</th>
<th>Pharmacogenetic Result Described to Parent</th>
<th>Actionability</th>
<th>Cases</th>
<th>Controls</th>
<th>Total (n=61)</th>
</tr>
</thead>
</table>
| Poor Metabolizer | - Child’s 2 CYP2D6 genes do not work | - Codeine will probably not work to lower child’s pain  
- Doctor should not give codeine to child | 1 | 0 | 1 |
| Extensive Metabolizer | - Child’s 2 CYP2D6 genes fully work | - Normal dose of codeine should work to lower child’s pain  
- Child is not at increased risk for side effects with normal doses of codeine | 9 | 8 | 17 |
| Extensive Metabolizer (2A-2A) | - Child’s 2 CYP2D6 genes that fully work  
- Some reports suggest that the differences found in child’s CYP2D6 genes may cause [him/her] to make extra enzyme  
- Until more evidence is collected, our laboratory reports CYP2D6 gene results like this as normal. | - Normal dose of codeine should work to lower child’s pain  
- If codeine is needed, be alert for possible side effects from normal doses of codeine | 3 | 1 | 4 |
| Intermediate Metabolizer | - 1 CYP2D6 gene makes normal amount of enzyme and one gene makes enzyme that does not work as well as expected  
- 1 CYP2D6 gene makes normal amount of enzyme and one gene does not  
- 2 CYP2D6 genes make enzyme that do not work as well as expected  
- 1 CYP2D6 gene does not make enzyme and 1 CYP2D6 gene makes an enzyme that does not work as well as expected | - Normal doses of codeine may not work as well as expected to lower pain  
- Not an increased risk of side effects from normal doses of codeine | 17 | 22 | 39 |
| Ultra-Rapid Metabolizer | - Child has at least 3 CYP2D6 genes that work well  
- More genes mean more enzyme | - Normal doses of pain medication, like codeine, should lower pain very well  
- Increased risk of side effects  
- Doctor should not give codeine to child | 0 | 0 | 0 |
<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Cases (parents of children who were previously exposed to opioids)</th>
<th>Controls (parents of children who are naïve to opioids)</th>
<th>Number (n=61)</th>
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<tbody>
<tr>
<td><strong>Parental Identity</strong></td>
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<tr>
<td>Mother</td>
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<td>Father</td>
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<td>Adopted Mother</td>
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<td>Adopted Father</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>20-29</td>
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<tr>
<td>30-39</td>
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<td>50 and up</td>
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<tr>
<td>Black or African-American</td>
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<td>Other</td>
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<td><strong>Education</strong></td>
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<td>High school graduates or have their GED</td>
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<tr>
<td>Some college or a 2-year degree</td>
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<tr>
<td>4-year college graduates</td>
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<tr>
<td>More than a 4-year college degree</td>
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<td>10</td>
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<td><strong>Income</strong></td>
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<tr>
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<tr>
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<tr>
<td>$25,000-49,999</td>
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<td>6</td>
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<td>$50,000-74,999</td>
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<td>$75,000-99,999</td>
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<td>More than $100,000</td>
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<td><strong>Employment</strong></td>
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<tr>
<td>Unemployed</td>
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<td>Worked in healthcare, healthcare related industry, or in biomedical research in the past</td>
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<td>16</td>
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Table 3

<table>
<thead>
<tr>
<th>Code</th>
<th>Illustrative Quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Help child</td>
<td>“I think definitely it’s something that he would know when he will be having something that is quite painful, that that medication in that form is maybe a great thing for him that would be able to control the pain if he needs it in that aspect. It’s nice to know because there are people who cannot have their pain controlled well, and it is nice to know if you do need it for something significantly painful, that’s it’s there. I think it’ll be very beneficial in the future. Hopefully he won’t have to use that knowledge, but sooner or later it seems like we all do. It’s great to be there for him.” (C-EPS 032)</td>
</tr>
<tr>
<td>Help others</td>
<td>“…you never know, especially with medications and such, there’s always new treatments and everything coming out through the course of his life that something we had done, say, to see his genetic makeup that could possibly make a difference in his future treatment.” (C-EPS 084)</td>
</tr>
<tr>
<td></td>
<td>“For me, it just means better healthcare for my child, knowing how her body processes the drugs.” (CEPS-111)</td>
</tr>
<tr>
<td>Contribute to</td>
<td>“Because I could help other people with possibly medical solutions…” (C-EPS 023)</td>
</tr>
<tr>
<td>research</td>
<td>“Because my mom has adverse reaction to morphine and I thought that doing these studies on morphine and how the body reacts to it would benefit people.” (C-EPS 024)</td>
</tr>
<tr>
<td></td>
<td>“…I always like being able to help when we can help.” (C-EPS 068)</td>
</tr>
<tr>
<td>Trust CCHMC</td>
<td>“Anything that would be research into why people react the way they do is valuable.” (C-EPS 024)</td>
</tr>
<tr>
<td></td>
<td>“Because I am a nurse and a mother, and feel like when you have research, that’s what make healthcare and disease process just more understood.” (C-EPS 038)</td>
</tr>
<tr>
<td></td>
<td>“I guess because just to help out the research…” (C-EPS 095)</td>
</tr>
<tr>
<td>Learn about health</td>
<td>“I guess because they asked us to and it didn’t seem like it was going to be that big of a hardship.” (C-EPS 045)</td>
</tr>
<tr>
<td></td>
<td>“I’m happy that we have Children’s Hospital in Cincinnati, and I know you need the research to be able to do that, and I have health kids and we can participate, so that’s good.” (C-EPS 072)</td>
</tr>
<tr>
<td></td>
<td>“I’m impressed every time we come from ___ to Cincinnati Children’s Hospital who has ___ here in Atlanta, we really are travelers, so we’ve come there since A___ was probably two or three years old, and he’s seven now, and we really believe in what you guys are doin’, and you guys are doin’ a great job.” (C-EPS 126)</td>
</tr>
<tr>
<td></td>
<td>“To be more informed and get the results of how it turned out about T___ and how she would handle pain medicine.” (C-EPS 029)</td>
</tr>
<tr>
<td></td>
<td>“I just think it’s a better awareness of his health. He has to acknowledge that anything he takes, even if he thinks he’s got a headache, that everything interferes with your body. It’s all chemicals, and changes happen, and he should be aware at an early age if he has to be concerned about somethin’ or not, and no matter what he drinks or eats or medication, it all has somethin’ to do with his body.” (C-EPS 074)</td>
</tr>
<tr>
<td>Code</td>
<td>Illustrative Quotation</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Child is normal</td>
<td>“That he would be OK to get a normal dose of pain medication, that he should react the way the medicine is meant to react.” (C-EPS 034)</td>
</tr>
<tr>
<td></td>
<td>“I feel somewhat relieved. It’s not often that we get a quote “normal” results. It was a relief that we found that out. We can rest easy that he’s OK genetically, it seems, with the codeine. I understand there are other side effects for other reasons, but genetically it looks like he’s OK.” (C-EPS 126)</td>
</tr>
<tr>
<td>Changes nothing</td>
<td>“…I’m not gonna look at him any different because he can’t take codeine.” (C-EPS 052)</td>
</tr>
<tr>
<td></td>
<td>“…I don’t feel like—now I know better how to—like, if he needs pain medicine, I know what to give him, so I feel like that is better, but I don’t think it’s going to influence anything…” (C-EPS 082)</td>
</tr>
<tr>
<td>No prior expectations</td>
<td>“I don’t know that I had any true expectations. I wanted to learn as much as possible, and when they said that they were gonna do a gene study to find out how ___ might react to some medicines, I was interested in finding out what the results of that might be so we don’t give him medicines that aren’t effective, things that aren’t gonna work. I didn’t really have any expectations, because I didn’t know what to think about it.” (C-EPS 021)</td>
</tr>
<tr>
<td></td>
<td>“I didn’t have any expectations of what I was gonna learn.” (C-EPS 029)</td>
</tr>
<tr>
<td>Expected/unsurprising</td>
<td>“They were pretty much what I expected to learn.” (C-EPS 024)</td>
</tr>
<tr>
<td></td>
<td>“I think it was pretty much what I expected to learn. I think I kind of understood what they were looking for when they were doing the research, and I had seen the way my son responded with the medication they had given him. So I pretty much wasn’t surprised when she told me that they found that that works well for my son.” (C-EPS 032)</td>
</tr>
<tr>
<td>“Fine”</td>
<td>“It’s no result that’s gonna cause a big life change for R__ or anything. It wasn’t bad news, it wasn’t good news, it was just, “OK.”” (C-EPS 039)</td>
</tr>
<tr>
<td></td>
<td>“I feel fine. I feel educated and this may come in handy at some point.” (C-EPS 083)</td>
</tr>
<tr>
<td>Information interesting</td>
<td>“I’m glad to know that. I was happy to learn that and understand it a little better. It seems like something that you can always keep in your mind. It also gives you the understanding that potentially in the future that would be something I could find out for my other two children if things would dramatically impact their pain control or even maybe some other areas that we don’t know yet. I found it very beneficial and interesting.” (C-EPS 032)</td>
</tr>
<tr>
<td></td>
<td>“Like I said, the information was definitely interesting. Science always offers a lot of stuff that you never really thought about before, so it is encouraging that they’re looking for better and more effective ways to treat pain and things like that. That’s always a plus.” (C-EPS 068)</td>
</tr>
<tr>
<td>Seek information</td>
<td>“I was interested in finding out about different diseases, if he would be at risk for anything, either now as a childhood disease or further on down the road as an adult.” (C-EPS 081)</td>
</tr>
<tr>
<td></td>
<td>“I’m just hoping that we’ll learn some more. That would be great. Especially, I still think it would be cool if we found that there was an incidental finding that would explain some of her medical issues. No one’s found anything like that, from what I hear from other people who have gone through those tests, but especially in a case like our daughter, where she’s adopted, we don’t have a genetic history that we know of. We don’t really know what’s in the background. So anything like that would be of benefit for us.” (C-EPS 129)</td>
</tr>
<tr>
<td>Worry</td>
<td>“I was a little concerned, because I really wasn’t sure—I mean, I knew it had something to do about pain management, but I wasn’t sure what exactly, and I was a little, like, leery, like, “What if I learn something really bad?” (C-EPS 003)</td>
</tr>
<tr>
<td></td>
<td>“I guess a little bit worried, just wondering if there could be more things that I could find out that might just make me worry a little more. It’s something that makes you think. Do you want to know, or do you not want to know? I don’t know if it’s good knowing ahead of time and worrying yourself and worrying them, or would it be better to know and prepare yourself for what may lie ahead. You’re kind of torn either way.” (C-EPS 005)</td>
</tr>
<tr>
<td>Surprise</td>
<td>“Oh, I learned a whole lot more than what I was expecting.” (C-EPS 082)</td>
</tr>
<tr>
<td></td>
<td>“…the specifics were surprising to me, the detail that they were able to find out.” (C-EPS 121)</td>
</tr>
<tr>
<td>Code</td>
<td>Illustrative Quotation</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Improve decisions</td>
<td>“In some instances, it would give you choices about what to do and even if there isn’t anything you could do, you would at least be sort of forewarned.” (C-EPS 017)</td>
</tr>
<tr>
<td></td>
<td>“I think about prevention. I feel like if somebody knows some information that would help me live a healthier lifestyle, would help me to make better choices, that I would want to option to know that information. Whether I decide to do something about it or not is a different story, but I would like the option to know…” (C-EPS 053)</td>
</tr>
<tr>
<td></td>
<td>“That you make better decisions about how you live your life if you know, the choices you make for your health.” (C-EPS 064)</td>
</tr>
<tr>
<td>Advocate</td>
<td>“...We have to be our own advocates medically more and more, and I think genetic results put us in that position of understanding more about ourselves, in a way that the doctor may or may not be able to tell us up front if we don’t share that information with him. You’ve got to be able to process your own medical information.” (C-EPS 003)</td>
</tr>
<tr>
<td></td>
<td>“It would be selfish, but you would be more interested in finding—funding research and everything. If you have the possibility of developing dementia, you’re gonna want to find a cure for that.” (C-EPS 075)</td>
</tr>
<tr>
<td>Info good</td>
<td>“If she had a predisposition to heart disease, she could make sure that she led a healthy lifestyle as a child into adulthood, always keeping that in the back of her mind.” (C-EPS 121)</td>
</tr>
<tr>
<td></td>
<td>“Knowing what could be coming, whether it’s treatable or untreatable at that particular moment in time, is going to be a benefit to the parents and to the child’s pediatrician, potentially, so that you can be on the lookout for symptoms and catch those much earlier than maybe you would otherwise.” (C-EPS 124)</td>
</tr>
<tr>
<td></td>
<td>“And it would sure be nice, if you knew that you had that, or that the probability was high that you would start experiencing whatever it is, it would sure be nice to know that if you read or hear about a particular study going on, you could participate, or you could have early intervention, just by virtue of the fact that you’re aware that that condition is a possibility, or is likely.” (C-EPS 129)</td>
</tr>
<tr>
<td>Code</td>
<td>Illustrative Quotation</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Stress</td>
<td>“It could cause stress if you don’t know what to do with the information, if you have to make a decision about what to do with it.” (C-EPS 018)</td>
</tr>
<tr>
<td></td>
<td>“The worry, the fear, if you let it take over your life, if you’re one of those types of individuals who will sit there and dwell on the negative, as opposed to figuring out how to handle it.” (C-EPS 019)</td>
</tr>
<tr>
<td></td>
<td>“…I would feel helpless, and I then I would want to treat her differently, and there’s a reason to treat her differently if I can’t—it’s like knowin’ the future, and I don’t like that.” (C-EPS 023)</td>
</tr>
<tr>
<td>Shock</td>
<td>“I think the harm would be more on the emotional side, if you’re finding something out that you didn’t expect to find.” (C-EPS 123)</td>
</tr>
<tr>
<td>Insurance</td>
<td>“…I would be very concerned about that information going into a medical record. If the information, for example, if it says you’re gonna get Alzheimer’s and it goes into your medical record, will there be a day when they will deny you service, because, “You know what? You’re gonna get Alzheimer’s anyhow, we’re not gonna do this whatever treat. It’s not gonna be of any value to you.” (C-EPS 003)</td>
</tr>
<tr>
<td></td>
<td>“I’m not sure, but I don’t know if insurance companies could find these things out, if that could be used against you because you could be discriminated against by insurance companies, but I’m not sure if insurance companies can even find that out.” (C-EPS 064)</td>
</tr>
<tr>
<td>Too narrow</td>
<td>“There are other factors besides just the genetics, and those factors are not something I’m educated to interpret, educated to know about…” (C-EPS 003)</td>
</tr>
<tr>
<td></td>
<td>“Just because you might be at a higher risk of heart disease, that doesn’t mean you’re gonna get heart disease. There’s people who die of lung cancer who have never smoked a day in their life. Sometimes you cannot control the outcome. So if it’s something—you can’t fix something if you don’t know it’s broken, so if you know, you can at least try to do what you can.” (C-EPS 072)</td>
</tr>
<tr>
<td></td>
<td>“…Knowing the medical condition I have with rheumatoid arthritis and seeing other people ___ in later years and understanding the side effects or whatever they go through, it doesn’t necessarily mean that’s what I’m going to go through, too. Each person is different. I don’t really think that adds a lot more stress, because situations change every day. Who knows what other factors could be playin’ in with your health, environmental or otherwise?” (C-EPS 074)</td>
</tr>
<tr>
<td>Untreatable bad</td>
<td>“Other things? If you found out other things? I think it’s beneficial if I can help her. But if I can’t help her in any way, shape, or form, I don’t think it’s beneficial at all. I would feel helpless if I couldn’t help her, and I feel like I would treat her differently than I would had I not known that she had it.” (C-EPS 023)</td>
</tr>
<tr>
<td></td>
<td>“If it were something that’s untreatable and incurable and maybe is happening later on in life, I don’t think that I would like to know that. I think it would be too much information and I would worry about it all the time.” (C-EPS 052)</td>
</tr>
</tbody>
</table>
References


gim2012176 [pii]


peds.2010-0938 [pii]


Appendix 1:

(These exact prompts may or may not be used. The person conducting the interview will be different from the person who discusses the results and conducts the quantitative survey.)

1. Why did you decide to participate in this study?

2. How did today’s information compare to what you were expecting to learn?

3. How are you feeling after learning about your child’s results?

4. From your perspective, what do your child’s results mean for your child?
   a. Is there an influence on health? Why or why not?
   b. Could these results influence how your child views his or her self? Why or why not?

5. How will the results affect your interactions with your child? (Potential Probes: Will these results affect how you care for or approach any health issues with your child? Why or why not?)

6. Do you plan to share your child’s results with anyone?
   “No” – Why?
   “Yes” – Who and why?

7. What recommendations do you have for us to improve the process of communicating genetic research results?

Intro: You may remember from the survey that some genetic tests used in research may search many genes at one time. These tests may reveal genes important for how a person responds to certain medicines. These tests might also reveal genes that may increase a person’s risk for developing a certain disease (like heart disease, cancer, Alzheimer’s, etc.). When these genes are not the focus of the research study but are found accidentally because of the way the genes were looked at for a study, we call them incidental results. These incidental results may reveal risk for diseases that could show up during childhood. The risks may be for diseases that could show up later during adulthood. Genes can reveal risk for possibly getting diseases that are treatable or untreatable. The next two questions relate to these types of incidental findings.

8. What do you believe could be the benefits of learning incidental finding results from genetic research studies?

9. What do you believe could be the harms of learning incidental results from genetic research studies?
10. How would you like to receive genetic research results about your child in the future if they become available?
Appendix 2:

Code Book

Themes/Codes

A. REASONS. This theme primarily focuses on the initial question about why participants agreed to the study, but some of the codes below are referenced by participants throughout their interview. Codes here are NOT exclusive; more than one can apply.

1. Help Child – Use this code when participants indicate that the information they receive will help them make medical/health decisions for their child.

2. Help Others – Use this code when participants indicate that altruism, doing good, or helping others was a motivation for their participation.

3. Contribute to research – Use this code when participants indicate that they are specifically trying to contribute to medical research. Right now, it seems like this code will often accompany (1) or (2), but future interviews might not maintain that trend.

4. Trust CCMHC – Use this code when participants indicate that they participated specifically because of CCHMC, its reputation, its clinical care, its research profile, etc.

5. Learn about health – Use this code when participants indicate generically that learning some “information”; often (but not always) this is information about health generally, their child’s health, or (rarely) their health.

B. EXPECTATIONS/REACTIONS. This theme arises from answers to the early questions about expectations for the information and reactions to the information received, but the answers to those early questions are repeated across the interview. Codes here are NOT exclusive; more than one can apply.

1. Child is normal – Use this code when participants indicate that the results did not show any altered CYP2D6 genes or drug metabolism. This is indicated by declarations that “my child is normal” and “the test said there’s nothing wrong,” among similar remarks. (In other words, the two quotations provided are examples and not an exclusive list of material to which you apply this code.)

2. Changes nothing – Use this code when participants indicate that the test results will or have changed nothing in their behaviors or attitudes toward their children.

3. No prior expectations– Use this code when participants indicate that they had no idea what to expect from the test.
4. Expected/un surprising – Use this code when participants indicate that they were not surprised by the result or that the result fit what they were expecting researchers to find.

5. “Fine” – Use this when participant indicates that they are okay or “fine” with the results they received.

6. Information interesting – Use this code when participants indicate that returned results information is itself intrinsically interesting and that their participation was motivated solely by “interesting” info.

7. Seek information – Use this code when participants indicate that they were motivated to seek more information about the results, what they mean for her child, etc.

8. Worry – Use this code when participants indicate that the information caused them stress, or made them worry or be fearful for their child and/or themselves.

9. Surprise – Use this code when participants indicate that the information came as a shock or surprise.

C. INCIDENTAL BENEFITS. Use this to code discussion of the value or benefit of receiving incidental findings for the parent or their child. As you code this theme, pay attention to whether they talk about incidental benefits generically/globally or in reference to specific types of benefits, so we can consider revising/expanding our coding options here as needed.

1. Improve Decisions – Use this code when participants indicate that the information they received will allow them to make better decisions for their child and/or their child’s health in the future.

2. Advocate – Use this code when participants indicate that the information will allow them to be a better or stronger or more capable advocate for their child in future medical encounters.

3. Info good – Use this code when participants indicate that the information itself and the opportunity to receive it is a good in itself. TRY TO AVOID using this theme and the other three. This option is meant to be exclusive.

D. INCIDENTAL HARM S. This theme covers mention of the harms the information about incidental/additional findings could cause. As you code this theme, pay attention to whether they talk about incidental benefits generically/globally or in reference to specific types of benefits, so we can consider revising/expanding our coding options here as needed.
1. Stress – Use this code when participants indicate that the information and even the possibility of receiving more information might cause them stress, or make them worry or be fearful for their child and/or themselves.

2. Insurance – Use this code when participants indicate that they have concerns about how insurance companies might use the information to the detriment of themselves or their child.

3. Unmeasured and/or unanticipated factors – Use this code to indicate that participants felt that the information was focused on genetics, implying an unwarranted genetic determinism especially when discussing multifactorial disease, and ignored environmental or lifestyle factors contributing to risk. This could be a harm in that it would mislead parents.

4. Untreatable bad – Use this code when participants indicate that finding out about untreatable conditions could be especially bad.