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Stakeholders' opinions on the implementation of pediatric whole exome sequencing: Implications for informed consent

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Abstract

Advances in whole genome and whole exome sequencing (WGS/WES) technologies have led to increased availability in clinical settings. Currently, there are few guidelines relating to the process and content of informed consent for WGS/WES, nor to which results should be returned to families. To address this gap, we conducted focus groups to assess the views of professionals, parents, and adolescents for the future implementation of WES. The discussions assessed understanding of the risks and benefits of WES, preferences for the informed consent discussion, process for return of results, and the decision-making role of the pediatric patient. Professional focus group participants included bioethicists, physicians, laboratory directors, and genetic counselors. Parent focus groups included individuals with children who could be offered sequencing due to a potential genetic cause of the child's condition. On-line discussion groups were conducted with adolescents aged 13-17 who had a possible genetic disorder. We identified discrepancies between professionals and patient groups regarding the process and content of informed consent, preference for return of results, and the role of the child in decision-making. Professional groups were concerned with the uncertainty regarding professional obligations, changing interpretation in genomic medicine, and practical concerns of returning results over time. Parent and adolescent groups focused on patient choice and personal utility of sequencing results. Each group expressed different views on the role of the child in decision-making and return of results. These discrepancies represent potential barriers to informed consent and a challenge for genetic counselors regarding the involvement of pediatric patients in decision-making and return of results discussions.

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Background

Whole genome sequencing (WGS) and whole exome sequencing (WES) have the potential to identify the cause of previously described single gene genetic disorders (Lupski *et al.*, 2010; Ng *et al*., 2011; Bamshad *et al.*, 2011) and complex disorders such as intellectual disability and autism (Vissers *et al.*, 2010; O'Roak *et al.*, 2011). WGS and WES can also guide clinical management of disorders for which other standard treatments have proven unsuccessful, such as allogenic hematopoietic progenitor cell transplant in the case of intractable gastrointestinal disease and the addition of serotonin precursor for a twin-pair diagnosed with dopa-responsive dystonia (Worthey *et al.*, 2010; Bainbridge *et al.*, 2011). A recent report from the National Institute of Health Undiagnosed Disease Program (NIH-UDP) demonstrated that WES or WGS performed on 32 individuals was crucial for identification of the underlying diagnosis in six patients after previous negative clinical, pathologic, or biochemical testing (Gahl *et al.*, 2012). While these reports include isolated case reports or small populations of affected individuals, they nonetheless demonstrate the potential applicability of WES and WGS in clinical settings.

One barrier to the integration of WES and WGS into clinical care involves the management of incidental or secondary findings, i.e., results that are not related to the patient's clinical indication for testing. It is estimated that an average exome yields 30,000 – 40,000 variants, with 3-8 of these being clearly medically actionable (Biesecker, 2012). Most of these secondary variants represent heterozygous status for recessive diseases. Berg and colleagues (2011) outline a model for return of results by "binning" or categorizing incidental findings. The model includes three categories of incidental findings: medically actionable variants (e.g., Lynch syndrome, BRCA1/2), clinically valid findings (e.g., pharmacogenetic variants, carrier status), and variants of uncertain significance. This model could provide a basis for categorizing incidental findings in order to guide the informed consent process for sequencing, and for returning results to families.

There is considerable variability amongst experts with regards to which incidental findings should be returned to patients having whole exome or whole genome sequencing (Green *et al.*, 2012; Lemke *et al.*, 2012; Lohn *et al.*, 2012). Recent guidance from an American College of Medical Genetics working group suggests a list of genes and conditions for which known pathogenic mutations should be returned to patients who have undergone clinical WES or WGS (Green, *et al.*, 2013). The list includes conditions that have onset in both childhood and adulthood and the guidance recommends returning the results to all patients, regardless of age. These recommendations have lead to additional debate about informed consent, decision-making, and patient choice (McGuire, A.L, *et al.*, 2013; Wolf, Annas, & Elias, 2013).

Most of the research on the views of patients relating to return of results comes from studies addressing results obtained in research settings. In the past there has been considerable

debate amongst professionals about whether to return sequencing results, including incidental findings, in the research setting (Wolf, 2012; Tabor, Berkman, Hull, & Bamshad, 2010). Prior research suggests that individuals may base decisions about return of results on the strength of the association of the variant with disease, as well as the personal utility of the results (Bollinger, Dvoskin, & Kaufman, 2012). Interviews with families whose adult children had undergone WGS in a research setting revealed few concerns about loss of privacy and confidentiality, and most participants felt that the perceived benefits of the test would outweigh these risks (Tabor, *et al.,* 2012). The families also expressed a desire for flexibility in terms of how and when to receive results, as well as a choice in which incidental findings to receive. Both professionals and lay groups have cited logistical concerns regarding returning results over time, and appear to have discrepant opinions regarding whether patients should be given a choice aboutreturn of results (Townsend *et al.*, 2012).

Controversies relating to the return of sequencing results are further complicated when the patient or research participant is a child instead of an adult. Older statements and guidelines from professional organizations discourage genetic testing of children under the age of 18 for carrier status and adult-onset conditions, unless there is a clear medical benefit during childhood, and the child is able to provide assent (ASHG, ACMG, 1995; AAP, 2001; NSGC 1995). These policies draw upon the need to respect the autonomy of the child and simultaneously seek to mitigate the potential risks of individual genetic test results in children, such as the psychological impacts of uncovering genetic susceptibility to disease (McBride & Guttmacher, 2009). Experts have argued that the parent's decision to proceed with testing can violate the child's "right to an open future" by making available genetic information that the child, as an adult, might have chosen not to know (Davis, 1997; Ross & Moon, 2000).

An updated set of guidelines continue to support the recommendation not to test minors for adult-onset conditions, yet also acknowledge that in limited situations the psychosocial burden to the individual and family may justify this testing during childhood (ACMG, AAP, 2013; Ross, Saal, David, & Anderson, 2013). Variants for these conditions will be identified routinely as incidental findings when performing WGS or WES, and returning such results to families would be discrepant with these updated guidelines. Adding to the controversy, the new ACMG guidelines relating to return of incidental findings state that results showing a pathogenic mutation associated with a significantly increased susceptibility to adult-onset breast/ovarian cancer and hereditary non-polyposis colon cancer should always be reported by the laboratory, even if the patient is a minor.

Despite professionals' concerns of harm stemming from childhood testing for adult-onset disorders, there is scant empiric evidence of adverse psychological outcomes of testing (Wade, Wilfond, & McBride, 2010). Moreover, there is evidence that if given the choice, many parents would want their children tested for adult-onset disorders. Interviews conducted with parents who had been tested for BRCA1/2 mutations found that almost 50% of parents supported testing of minors for this adult-onset hereditary cancer predisposition syndrome (Bradbury *et al.*, 2010). Reasons for support of testing minors included the opportunity to foster preventative behaviors, individual right to test, and absence of harm in

testing. Another study involving parents whose children with developmental delay were participating in a genomic research repository documented that most parents would like to receive all individual findings, including those with uncertain implications or no clinical utility, citing personal utility and adeptness at dealing with uncertainty (Harris *et al*., 2012).

Because of the limited experience offering genetic testing to minors for adult-onset conditions, there is little empiric evidence regarding best practices for involving the child in the informed consent process. There is a large body of literature on involving children in decision-making in other contexts, in both research and clinical settings. Studies have shown that for the most part, adolescents and parents prefer that decision-making be collaborative, with the extent of involvement of the child varying according to age and maturity (Geller, Tambor, Bernhardt, Fraser, & Wissow, 2003; Miller, Reynolds, & Nelson, 2008).

Given that little is known about how patients view the incorporation of sequencing into clinical care, this study assessed the views of adolescents, parents and professional stakeholders regarding the risks and benefits of pediatric whole exome sequencing, preferences for the informed consent process, attitudes towards return of incidental findings results, and the process of disclosure. Attitudes regarding the involvement of the pediatric patient in decision-making both for pre-test consent and return of results disclosure were also assessed. The overall aim was to develop an informed consent process for offering sequencing and returning results that would be responsive to the needs of patients, family members, and health care providers. This project was conducted as part of a larger NIH-funded project in which WES is being offered to groups of patients, and the outcomes of testing assessed.

Methods

Three sets of focus groups were conducted, one with professional stakeholders including clinicians (physicians and genetic counselors), laboratory directors, and bioethicists; a second with parents of children with disorders for which sequencing may be offered as a part of the CHOP study including bilateral sensorineural hearing loss (BLSNHL), nuclear encoded mitochondrial respiratory chain disorders (NEMRCD), sudden cardiac arrest/ sudden cardiac death (SCA/SCD), and autism spectrum disorders (ASD); and a third set of on-line discussion groups with adolescents aged 13-17 affected by BLSNHL, NEMRCD, or SCA/SCD. The study was approved by the Institutional Review Board of the University of Pennsylvania.

Participants

Potential professional participants from universities and hospitals in Philadelphia, PA and Baltimore, MD were identified by one of the authors (BAB) and recruited via e-mail. They included clinicians, bioethicists, lab directors, and genetic counselors. A total of 51 professionals from Philadelphia, PA and 43 from Baltimore, MD were sent an e-mail invitation to participate in the study. Seventeen (33%) people from Philadelphia and 13 (30%) from Baltimore indicated interest in attending a focus group and a total of 22 (23%) participants attended the scheduled sessions. Additional demographic information is available in Table I.

Potential parent participants were eligible if they had a child who received care for a target disorder through specialty clinics at CHOP including hearing loss, mitochondrial disorder, cardiology, and the Center for Autism Research. A total of 199 recruitment letters were mailed to parents/guardians of the clinic patients. Responses were received from 29 (15%) parents and 20 (10%) attended one of two focus groups, both of which were held in the Philadelphia area (Table I).

Adolescent participants were recruited from CHOP specialty clinics through letters sent from clinic directors to parents. In order to participate, adolescents were required to be capable of managing the technology needed for the on-line discussion and comfortable communicating by reading and writing English. Parents were asked to discuss the focus groups with their children, and if interested, adolescents and their parents were instructed to contact study staff to discuss their availability. Interested participants were e-mailed parental consent and adolescent assent forms with focus group details. Parents and adolescents were required to return the signed consent and assent forms before being assigned to groups.

A total of 100 letters were sent to potentially eligible adolescents from the CHOP clinic. Three adolescents indicated that they were not interested, 5 indicated interest but did not return the signed consent document, and 7 (7%) participated (Table I). One adolescent focus group was conducted in June 2012 using AdobeConnect software. Each participant chose an alias and was e-mailed a link to the discussion group that was specific for his or her scheduled session. An on-line focus group format was chosen because its design is inclusive of adolescents with and without hearing loss, and because adolescents are generally accustomed to exchanging thoughts on-line.

Data Collection

Each face-to-face focus group included two moderators and two observers/note-takers. Focus group guides included topics to be discussed in addition to probes used to clarify and expand on participant responses. Focus groups began with a basic introduction to whole exome sequencing (WES) with language appropriate for each group. A fact sheet sent to participants provided a short overview of issues raised by WES which was reviewed by the focus group moderator during the introduction:

> “Whole exome sequencing is a new kind of blood test that looks at all the genetic material (DNA) a person has. The test would be used to figure out the genetic cause of many different types of disorders.”

The fact sheet also included information about the types of results that could be found on WES:

> “Sequencing results may also provide information about other conditions that are not related to the child’s disorder. These are called “incidental findings.” Incidental findings may include:
>
> - Information about the chance of developing certain treatable health problems in the future, such as cancer, heart disease or diabetes.

- Information about the chance of developing certain untreatable health problems in the future, such as Parkinson's disease or Alzheimer's disease."

The discussion topics were organized into sections, beginning with general reactions to WES and the perceived risks and benefits of clinical pediatric exome sequencing, followed by explanation of possible result categories (i.e., bins), assessment of preference for return of results, process for pre-test informed consent and results disclosure, and closing with the role of the child in decision-making. The focus group guides contained comparable thematic discussion topics and the level of complexity of language was tailored to the particular focus group population. Hypothetical "bins" of results included those pertaining to the child's presenting condition, adult-onset cancer predisposition with currently available screening and prevention, risk for an adult-onset disorder for which there is no proven prevention or treatment (e.g., Alzheimer disease), risk for young adult-onset psychiatric disorder (e.g., schizophrenia), and carrier status for diseases such as cystic fibrosis. Focus group participants were not explicitly asked about misattributed paternity or consanguinity that may be discovered as part of WES.

Data Analysis

De-identified transcripts of the face-to-face focus groups were produced from the audiotaped recordings. Note-takers present at the focus groups recorded the speakers and main topics of discussion. The on-line discussion group allowed for analysis of the typed transcript and included polls to quantify positions on certain topics, followed by probes to expand discussion. The polls were presented within the discussion group as pop-up windows, and adolescent were asked to select whether or not they would like to receive hypothetical results by responding with "yes", "no", or "I'm not sure." Within the discussion group, participants were asked to elaborate on the reasoning behind their responses.

A preliminary codebook was created with broad codes including: "benefits of sequencing, "risks of sequencing", "process of informed consent," "content of informed consent", "challenges and barriers to informed consent," "process for return of results", and "role of the child in decision-making". One of each of the professional and parent focus group transcripts were coded independently by two coders before coding of the remaining transcripts. Differences in coding were resolved by consensus. New codes were added to the codebook as needed. NVivo software was used for data coding and analyses. After all transcripts were coded, the investigators reviewed all codes to identify dominant themes. Representative verbatim comments were selected for presentation.

Results

Analysis of the broad codes revealed areas of similarity and dissonance between professional and patient group opinions regarding the process for informed consent, content of informed consent discussions, preference for return of results, process for return of results, and the role of the child in decision-making. These results are reviewed below and quotes illustrating major findings are included. Quotes from parents are indicated by "PA", professionals by "PR", and adolescents by "AD".

Process of Informed Consent

Both professional and parent focus groups identified factors that might serve as barriers to informed consent for WES in the clinic setting, including the need for time for discussion beyond the scope of a clinic visit and possible distractions due to the presence of the child. To address this barrier, parents suggested sending informed consent documents out before the clinic visit, but overall most parents agreed that the informed consent discussion did not require an appointment separate from the clinic visit. One parent said:

> PA11: "You'd need to have the consent form sent to the house so you could actually read it… there's nothing worse than getting somewhere and having to make a critical decision like that on the spot… I think it would actually be somewhat unethical to have that medical knowledge being offered without the patient understanding the depth of the decision they're making."

Professionals and parents also agreed that a key challenge to informed consent discussion was the complexity of WES itself. Professionals expressed concern regarding the technical and interpretative limitations of the test and poor patient understanding, given prior experience with single gene testing.

> PR10: "…how difficult it is for people to understand things like risk information, how difficult it is for people to understand results that are not clear cut, i.e., variants of uncertain significance…"

Parents reported concern over complexity compared to other types of medical testing:

> PA02: " It's not an x-ray or an MRI, something simple that people can understand. An MRI, here, you got pictures, you can see. This is something that is still science fiction I think to a lot of people, complicated."

Professionals, parents, and adolescents had divergent views on the extent to which the child should be incorporated in the informed consent discussion. Most parents indicated that they would like to be given a choice about the extent to which the child would be involved in the informed consent discussion.

> PA17: "…So I would expect to get a pre-appointment consent form and maybe one of those boxes is, "do you want your child involved in the conversation or do you want your child included in the decision-making as to what information they get and don't get.""
>
> PA11: "I agree completely."
>
> PA12: "Absolutely."
>
> PA14: "Good idea."

In the event that the child refused to undergo WES, some parents indicated that they would authorize proceeding with WES, either because they believed it to be in the best interest of the child, or for altruistic purposes. This husband and wife discuss decision-making:

> PA11: "We make the choice for our daughter. She really has no – no say. To be – participate in a research study, it would depend on how involved it was. If it was simply a blood draw, I would say – I would present it as somewhat not optional. I

mean not that I would force her. But to me, I would say this is something you need to do and this is what we're gonna. She's very easy-going."

PA12: Amenable.

PA11: "Amenable and you know, very manipulable."

PA12: "In a good way."

Moderator Two: "What's the reasoning for that, for you to say – to present it as not optional?"

PA11: "Because I think it's for the betterment of man, and I think – because the doctors need to study it."

Conversely, adolescents felt that the child and parent together should make the decision whether or not to have sequencing, and that involvement of the child would depend on the child's age and maturity. Reasons for involving the child centered on the child's right to know.

AD03: I said both should decide together, because both parents and kids have a role in the testing. Therefore, their voices should be heard.

AD05: It's a child's body, so they should have a say. Then again they may be too young to make a decision on their own, so the parents should also help. I think it's important for the two to agree.

Professionals raised concerns about allowing the child to be absent from the decision-making process, and most agreed that the child would need to be included in the discussion in the context of a clinical research study.

PR02: "And IRBs are gonna say it's up to you to decide…It's up to the individual investigator to decide, do I weigh this kid's assent or not. But I'd argue that for non-therapeutic testing, which is what this is, your threshold has to be pretty damn high not to include this kid, irrespective of what the parents say.

Most professionals, parents, and adolescents agreed that the level of involvement of the child would depend on factors such as age and maturity. Professionals commented that each family would make these decisions differently, and that there would be no "one size fits all" approach for implementing WES in pediatric clinical settings.

Professionals also acknowledged that the capacity for decision-making might depend on the child's experience with healthcare settings.

PR02: "…And no single child is alike. And that's good. And that's bad. I think that gives us – sometimes we err on being too cavalier in what we expect of these kids. But in general, the seasoned, more experienced kid, who's been through the proverbial ringer, has had more experience with decision making, is gonna have more capacity than my eleven-year-old daughter at home, who I'll let decide what she wants to wear to school, maybe. But I think we also need to – it's very important for us to know what kind of history of decision making have the parents given the kid who you're talking about thinking to include in this decision or not,

> because if it's just the kid who gets to decide what shoes she wants to wear to school versus the kid whose parents have given them a life of participating in some type of meaningful decision, I may decide that I'm gonna include that kid more than the first one.

Another potential barrier to informed consent identified was the automatic acceptance of sequencing because of parents' desire to know the cause of their child's condition and the child's prognosis. Both parents and professionals acknowledged that parents are likely to immediately accept the offer of WES without carefully considering the issue of incidental findings. This parent discussed her interest in WES as a possible diagnostic tool:

> PA13: I think it would be great, because I know for me, with [child]… no one really has the answer, because nothing's tied in together, that if there could be a test where we could pinpoint it better, and again her future health…if there was something to give me more of an answer, or call it a name and tell me what is her future gonna be or what are we gonna be, I would jump on that in a heartbeat.

Likewise these professionals reported how their experiences led them to anticipate potential automatic acceptance of WES without careful consideration of the risks and limitations of sequencing:

> PR15: "…So in a mitochondrial disease clinic I know that people are literally dying for a diagnosis. So they're not gonna stop. It's almost irrelevant what else you find, because generally those patients are so sick it doesn't matter. In a hearing loss clinic, you havepresumably a healthy population who has hearing loss. And so the risks and benefits of the information they will glean is very, very different."

> PR24: "The types of patients I see are some that will be included here, who will – they have had years, very sick kids that are developmentally very delayed, very sick, lots of problems, and they have been through years, and thousands of dollars of testing…So I feel like so many of the families we see are so desperate for information…"

> PR10: "Information is better, more is better."

> PR24: "… parents are so desperate for any answer for their kid, because they think that it will come with a cure or a treatment plan or at least recurrence risk counseling, which is important.

> PR25: Or sometimes just a name is helpful."

Content of Informed Consent

Discussion of components to include in the informed consent session revealed key differences between professionals, adolescents, and parents. Few parents and adolescents indicated interest in learning about genetic concepts or genomic variation. Adolescents almost exclusively focused on the practical aspects of the test: number of tubes of blood, amount of pain, and what the test would involve. Parents brought up concerns about the potential risks of participation in genetic testing, including stigmatization, discrimination in both insurance coverage and employment, loss of privacy, and possible restrictions on future

reproductive decision-making for the child. This parent talked about her concerns about her child having to choose a partner based on knowledge of his/her genetic make-up:

> PA09: Maybe I would know, but then I'd kind of feel an obligation to tell them. Then I really wouldn't want them to make decisions, like partner, life-long partner decisions based on if their partner has the same genetic pattern.

Most professionals also acknowledged concern for discrimination and stigmatization. However, professionals also expressed concern that family members, including parents, might stigmatize the child if he or she was found to be at high-risk for an adult-onset, untreatable disease or cancer predisposition.

> PR12: "…Parents may treat a child differently. I think you're more likely to get some horrible disease, or you're gonna be my healthy child that's gonna take care of my old age and you'll be the one that's gonna be affected. I just think that there's weight to that…"

This parent commented on the burden of having information about the future health of her child, and on the difficulty of making decisions regarding sharing that information:

> PA11: " Because if you know your child could get – would have Alzheimer's, early onset Alzheimer's at 50, do you tell them? I mean that's awful. Just think of all the joy that would remove from your life until they turned 50 and started to lose their mind. That'd be awful"

Almost all professionals agreed with including a discussion of the limitations of WES in the informed consent. Different types of limitations were discussed, including what information the test could not provide families, the possibility of not finding the cause of the child's condition, and the challenges of evolving interpretation. Concerns about these limitations were notably absent in the parent groups, though one participant mentioned that the test may not find a genetic cause for the child's current condition. A few parents and adolescents did, however, indicate that they would like to have information on the certainty of results and accuracy of the test itself, specifically related to how the samples were handled and the potential for laboratory error. Some professionals had concerns that poor patient understanding may lead individuals to believe that the tests covers all genetic conditions, whereas current technology may not detect trinucleotide repeat conditions, such as Huntington disease:

> PR07: "…people who don't actually work with the data sort of assume that the test gives correct results all the time. But the closer you are to it, the more you realize that there are limitations. And I would worry about people being oversold."

> PR16: And I think another issue is letting them know what this doesn't test for. In other words, oh good I don't have Huntington's, well we're not really testing for that.

Discussion of the implications of the child's WES results to the parent was absent from parent focus groups, rather the discussion was focused on receiving results on the child, and the possible impact of results on their other children or future grandchildren. Though some parents indicated that WES results could help to explain family history, very rarely did the

parents anticipate that WES could provide information related to their own current or future health.

Preferences for Return of Results

Most parents and adolescents stated that they would hypothetically want to receive all results from WES, including those relating to the cause of the child's current condition, cancer pre-disposition, carrier status, and adult-onset, untreatable disease. Reasons for wanting such results included the opportunity to prepare for the future, the possibility of further developments in medical treatment and prevention, and the belief that they were entitled to all sequencing data. In addition to elucidating disease course and the possibility of therapeutic benefits, some participants cited personal utility as a reason to receive information related to adult-onset conditions:

> PA01: " See I would like to know all the high risks, whether I can do something about it or not, just – I don't care about the ten percent or one percent, but high risks, even if you can't treat it, I would like to know that. Just so I can prepare."

> AD05:I would like to know what to expect. Not just suddenly get sick and not know why, I would also want my family to be ready for what may happen to me.

Only a few parents would be opposed to receiving results for carrier status and adult-onset untreatable conditions. These parents expressed concerns about potential restrictions on the child's reproductive future, anxiety, and risk for other discrimination and stigmatization. This parent provides an example of potential insurance discrimination:

> PA12: "… I send along my genetic testing sorts of things and Blue Cross Blue Shield pays for it, and I think it's disingenuous to say that an insurer, whether it's a private insurer or the government or whomever, is not going to say – geez, you know we saw that you had this result of 60%, 80 %, 10 %, here's a pamphlet on how to prevent Down syndrome. Here's a pamphlet on how to prevent ALS. And it's not who's picking up the bill. It's what they're gonna do with it afterwards."

Some parents expressed that although genetic information holds the potential for discrimination for their children in the future, this risk might not outweigh the benefits of having the opportunity to gain as much knowledge as possible from the sequencing test:

> PA18: "I want to know and I would like to have all the information that I can to make decisions from there. And even saying this I think I would still err on the side of wanting to know. But say that there is something like bipolar or schizophrenia markers that pop up. Is that something that, say my son wants to go in the FBI one day. Is that something that could ever potentially be brought up? I mean it's definitely a concern. Does the benefit outweigh the risks of that? Possibly, I think so."

This concept of weighing the risks and benefits – in this case, the burden of knowing versus the possibility of therapeutic benefit – was mentioned by this same participant earlier in the session:

> PA18: “I think too, I definitely agree with – it’s definitely a heavy burden if I know this and I know this is coming, do I share it? Do I want to know, even after I know, I can’t take that away. But I think for me, having that knowledge and what you said as being able to do anything to prevent it or prepare for it. If I had the option and I said, oh I didn’t know that and I could have done X, Y and Z, I think that might personally, for me, be the heavier burden. If there was any vitamins, drugs any further testing.”
>
> PA20: “Knowledge is power.”
>
> PA13: “I was just gonna say knowledge is power and to me I’d rather, the good, the bad, the ugly, I’d rather know it all…”

Some participants also mentioned that electing to not have the test or receive additional results could be a burden in itself, in that it could be seen as a missed opportunity:

> PA11: “There is a burden – there comes a burden with that knowledge that you could have had information.”
>
> PA15: “Changed something or maybe whatever the test results said would have changed something and made his life better or – somehow made his life easier.”

Most adolescents indicated a desire to receive results for untreatable adult-onset disorders, but one adolescent acknowledged that there were potential psychological risks of this information.

> Moderator: What if you couldn’t do anything to prevent the cancer, would you still want to know?
>
> AD06: I could live a good life and be prepared with my family, they love me and would stick by me and help me make good decisions.
>
> AD03: Probably not. I’d rather be surprised than know it’s coming, because that’s worse, to me…because if I can’t cure it, the anxiety of when it will come would make me sick.

All adolescents expressed interest in receiving results related to carrier-status, some to avoid having a child with the condition and others to be more informed about possible treatments.

> AD07: “I would want to know what my child would have to go through to become healthier.”
>
> AD03: “I said yes, I’d want to know, because then I wouldn’t have kids. I don’t want anything detrimental to happen to my kids.”

Overall, there was much less consensus among professionals regarding which results should be made available to research participants and patients. Professionals who did not support return of carrier status indicated that this should be offered to an individual in the context of reproductive decision-making, and that carrier status testing for minors is not supported by current guidelines. Some professionals supported the option to disclose carrier status to parents, particularly if the parents were planning to have more children.

> PR05: "… And the kids are the only people who need to know they're carriers, unless you've confirmed in the parents and found them both to be, in which case I would break that code and say you guys are both carriers for something and I know you're planning on more children. And I'd ask that question actually – if we find you're both carriers for something, do you want to know that?"

All professionals had concerns regarding return of results for adult-onset, untreatable disease and did not support this as an option. They cited the lack of outcome data on adolescents undergoing genetic susceptibility testing for adult-onset diseases, and the current guidelines that do not support testing children for adult-onset disease.

Professionals voiced questions about their professional obligation to return results that would be medically actionable for the parent, but not immediately actionable for the child. Most professionals expressed uncertainty about their obligation to return these results to the parent, especially in situations where the parent was not interested in learning results other than those directly relating to the child's current condition.

> PR10: "…I go back and forth all the time, because you've just identified a family who has this gene mutation, and penetrance can vary and due to limited family structure or people who died early of other reasons, it may not be apparent that this family has Lynch syndrome. So it could be hugely beneficial to identify that this family has Lynch syndrome, because there may be people right now, who need a whole variety of things. That could save their lives. So that's compelling, that's really compelling. And how, practically, are you going to get that information to them ten years from now when there are people at risk right now, you have to get it to them."

Several of the laboratory directors voiced concern about excluding from their report an actual finding just because the parents opted not to learn that result:

> PR13: "As a person from a lab, I feel trouble not putting in their reports something that I saw. Okay? Parents don't want to know, but it is there. So I'm not gonna tell anybody, I'm the only one who's gonna know that?…I have trouble with that."
>
> Moderator: "Is it your own distress that you would feel or is it an ethical, legal concern?"
>
> PR13: "I think it's both. I mean I think it's our obligation to spell out everything that we see."

More globally, many professionals expressed concerns about giving parents the choice in which results they could receive:

> PR22: "…what I hear too is if you're giving people a choice to hear the information, you're essentially setting up this dichotomy of who owns the information. And by giving them a choice you're gonna set up this system where parents are gonna feel they own the right to access that information. And then do we have the right to say no we – we as the practitioners – control access to that information. So I think the decision has to be made beforehand of whether they're

gonna be given a choice or not, so that you're able to put everybody on an even playing field."

Many professionals argued against allowing parents full choice in preference for return of results based on issues related to the child's autonomy as an adult. This stance led some genetic counselors to suggest that parents should not be given an opportunity to learn information beyond the scope of the child's current condition:

PR01: "… I want to just offer this out there as a possibility, that it's possible to take a stand here and say, we're testing for this, I appreciate that gasoline can be used for a lot of things. But I just want it to drive my car from here to here. So this test can be used for a lot of things, but here's why we're doing this and I'm not sure we're in a place where this is all worked out enough. I feel very nervous about all of this. So I'd rather go more slowly."

Conversely, most parents believed they should have the option to choose which results they would like to receive, and were against having restrictions placed by providers, a laboratory or a professional organization.

PA05: "…I would feel that there was some sort of agreement entered into as far as – if they would have some sort of knowledge about me and I asked where I would expect that I would be able to have access to it."

Process of Return of Results and Role of the Child in Disclosure

Parents agreed that results of WES should be returned in person, with a written summary of findings, and that they should be informed prior to the appointment which providers would be returning the results. Most parents would want to exclude the child from the results discussion so they would have time to process and understand information, and avoid potential harm to the child.

PA01: "I think parents have to process it before their kids can. Because if you get bad news and your kid's there and you're breaking down because you're told this stuff, it's not fair for your kid to see that. Like, you're supposed to be strong for them and you can't even process it because they're there. So I wouldn't want my child around if I got bad news."

If the provider were going to discuss the results directly with the child, some parents would want to know details about the content of that discussion

PA02: "…. For me, I would want to know the results first, to know, okay then discuss with the guidance person or whoever is gonna give the results, okay, well how are you gonna do this. Are you gonna just say the same thing to them that you told me? Or are you gonna be able to have things to explain it to them in terms they would understand?"

If the parent was tasked with discussing the results with the child, many parents would want guidance about how and when to have that discussion, and indicated that there would be a potential burden in having that information.

> PA11: “I mean that would be a really heavy weight to know, oh my gosh, she is – she has the genetic markers that she could end up with major heart problems or some other genetic carried issue. So then do you tell her? When do you tell her? Do you counsel her not to have children? I mean all these major decisions would come with it.”

Adolescents indicated that they would like to be a part of both the decision-making and return of the results process, but were concerned that their parents might not give them the full information relating to their current condition or other findings. They also expressed a desire not to be misled or lied to regarding their genetic test results, but realized that parents might not tell them the full information in order to protect them:

> AD01:I would think it would be for the better if they didn’t want to tell me then they obviously didn’t want me to know for a good reason. But I would be upset.

> AD02: I think that too and with my disease my parents usually keep me updated but when they don’t I get mad because its my body not theirs and I deserve to know.

> AD03: If the results are really bad, they wouldn’t [want] me to have it hanging over my head until something was done about it.

Some professionals indicated that if they were to “put on their parental hat” they too, like the patient participants, would want to receive sequencing results first before the results were shared with the child.

> PR15: “… As a parent I would absolutely want to digest whatever information you’re going to tell my child first before you tell my child. I have a really bright kid. But I need to digest – I need to get there – if you’re telling me something bad, I need to think about it, I have to get myself around it and then – you know, and then we’re gonna talk about it. That’s not a simultaneous disclosure. Absolutely not.”

Both parent and professional groups agreed that a two-step process for return of results would be optimal for WES. Participants in both parent groups spontaneously suggested this method as a way to avoid becoming overwhelmed with results. The first step in results disclosure would be to receive information relating to the child’s current condition, with a follow-up visit discussion of incidental findings.

> PA12: “…You try to put yourself in the shoes of coming in for a diagnosis and the doctor says well you know what it is, it’s X. Hey, by the way, let me tell you about the other five things that we’ve figured out. And if hearing the first thing is difficult for a parent, adding five more things isn’t gonna help the situation. So the subsequent information that you learn I think would absolutely have to be presented months, years down the line. Absolutely.”

Several parents suggested that some results should be held and returned to the family at some suitable time in the future:

> PA08: “you might kind of put the other results in a box that can be retrieved later on by either a parent or the child when it becomes old enough.”

Although professionals agreed with the model of releasing results when they might be medically actionable or scientifically understood, they expressed concerns about a professional responsibility to re-contact patients over time with changing interpretation of results due to scientific advancements. In the research setting, some recommended that there be a defined end to the study period after which results would no longer be returned. In the clinical setting, one professional suggested a model for return of results that would span across the lifetime of the individual:

> PR05: " there's a life course. Right? So it's very different – if you had in addition to bins you had those bins sort of tagged with a life course, so that actionable today versus actionable at reproductive – you know, that they're sort of, as much as you could, there are clear milestones on there, so that the clinician knows, okay, child is five, this isn't actionable until they're reproductive age. So that's not in that – you know what I mean. It's not gonna be one size fits all, because a five-month-old is very different from an 18-year-old."

Finally, some parents also indicated interest in receiving results according to the magnitude of disease risk conferred by the variant. Either the return of results report could include only higher risk variants, or patients could elect if and when they would receive the lower risk variants. Parents indicated that those higher risk disease variants would be better to know for future preparation, where the lower risks could be potentially less meaningful.

> PA12: But I think if you were to tell us well, it's 10 percent, it's 15 percent, what does that mean?…I guess what I'm saying is in terms of well it's gonna be ten percent 15 percent, so it's gonna be something. And it is absolutely useful to know. But just in the abstract, sometimes it's not useful. And if you don't know the context of it, it can engender confusion and distress amongst a family.

Parents indicated that they would like the results to be returned by a knowledgeable professional who has experience disclosing genetic information to patients. Parents would need time to process the information and ask questions, and some indicated interest in receiving support group referrals for any diagnoses. One parent suggested being placed in contact with other families who have also received WES results for their children.

> PA02: "I think peer groups might be – for people that they're suggesting to do this, to have peer contacts, other families that have gone through this already…Okay, what can I expect? What are the results? And obviously if it's somebody through CHOP, they're going to suggest people that have gone through it… So you've got another parent to talk to that's maybe not been through the exact same conditions that you've been, but you're not talking to a clinician or counselor – somebody from that end, you're talking to someone on your side."

Discussion

This analysis of focus groups of professionals, parents, and adolescents provides insight into several challenges and barriers to the process of informed consent and returning results from WGS and WES. All focus group participants acknowledged that WES is unique in the complexity and that pre-test discussions would require time and assessment of

understanding. Parents and professionals agreed that return of results should be administered in a two-step process with variants relating to the child's current condition variants taking precedence over findings not relevant to the child's condition such as carrier status. Parents preferred to have the option of whether or not to include the child in decision-making and return of results, while adolescents expressed a desire to be involved in both. Parent and adolescent participants would want to be given a choice about return of results and would find personal utility in information related to adult-onset conditions, including conditions that are currently untreatable. In contrast, most professionals would be opposed to returning results that would not be immediately medically actionable to pediatric patients and their families.

Much of the concern about offering WES on the part of professionals centered around the current limitations of WES in terms of technical capabilities (i.e., disorders tested for, percentage of exome coverage) and the changing interpretation of sequencing data over time. Parents and adolescents did not share these concerns and expressed little desire to be educated about the technical aspects of sequencing or genetics, potentially due to a limited understanding of genetics and the process of sequencing. Both professional and parent groups focused on the responsibility of the healthcare provider to make these results available, and to re-interpret results, over time. This is in contrast to the findings of Townsend and colleagues (2012), who reported that laypeople suggested that it is the patient's responsibility to contact their clinicians regarding new genomic developments. Pyeritz (2011) has suggested that to avoid burdening providers and the health care system, patients and family members should be responsible for contacting their providers about new developments, and that a discussion of handling results over time should be part of the informed consent process.

Professionals agreed that clinical WES becomes more complicated when applied in the pediatric setting, due to concerns over returning results related to adult-onset conditions. Current recommendations strongly discourage testing children for adult-onset conditions, unless there is a time-sensitive benefit to the child (ASHG, ACMG, 1995; AAP, 2001; NSGC, 1995; AAP, ACMG, 2013; Ross, Saal, David, & Anderson, 2013). However, a unique feature of WES is the incidental nature of some findings. These may be relevant to other family members, including parents and older siblings, which necessitates discussion over when and under what circumstances genetic variants present in both the child and a parent should be disclosed to the parent. Although nearly all parent and adolescent focus group participants would want all pediatric sequencing results returned to the family, prior experience has shown that patients can become saturated after 20-40 minutes of return of results discussion (Biesecker, 2012). Most professionals expressed concern over allowing parents to choose to receive results that would not lead to immediate changes in medical management. This highlights the conflict between professional and patient assessment of the utility of genomic information, and suggests that the views of patients and family members will need to be acknowledged as guidelines are developed for returning incidental findings from genomic sequencing, as has been recommended by Terry and Bonhomme from the Genetic Alliance (Terry & Bonhomme, 2013).

The parent focus group discussions provided information regarding how patients weigh the potential benefits and risks of medical testing and how they might include other factors, such as personal utility and the concept of "knowledge is power", which may be outside the scope of the clinician's traditional definition of utility. Consistent with other research (Facio, Edem, Fisher, *et al.*, 2012), parents demonstrated that they were able to distinguish between categories of results, and that they were cognizant of risks such as discrimination, stigmatization, loss of privacy, and additional anxiety in relation to receiving all sequencing results. But in the end, they felt that some of these risks would not outweigh the benefit of having the information and preparing for the future. Finally, there was an emerging discrepancy among the professional, parent, and adolescent participants regarding the level of involvement of the child in decision-making for testing as well as return of results. Professionals, drawing on experience in clinical practice and principles of medical ethics, acknowledged that assent for participation in WES, particularly in the context of clinical research, would be necessary for participation. A majority of parents, on the other hand, saw themselves as "gatekeepers" to their child's medical health information up to the age of 18 and expressed a desire to learn of results without their child present. Age and maturity were main factors discussed among parents and professionals as indicators of the level of child involvement, which is consistent with prior research related to other type of medical and research decisions (Miller, Reynolds, & Nelson, 2008). Also consistent with prior research, adolescents unanimously acknowledged that the child should have the opportunity for joint decision-making with their parents, given that the patient is at an age when he or she is able to make more informed choices about their healthcare: approximately 13-17 years (Broome & Richards, 2003; Dunsmore & Quine, 1995; Geller, Tambor, Bernhardt, Fraser, & Wissow, 2003; Miller, Reynolds, & Nelson, 2008). Importantly, professionals agreed that involvement of the child would need to be approached on a case-by-case basis.

Limitations

The results provided are a summary of the divergence and areas of consensus among the focus group participants, which are not representative of all professional stakeholders, parents, or adolescents for whom clinical sequencing is relevant. Particularly, the parents and adolescents who participated may be more eager to learn about advances in genetic testing and thus differ in important ways from parents and adolescents who chose not to participate. In addition, the very small number of adolescents who participated and the low participation rate of parent participants further limits what can be deduced from these groups' opinions. Because the aim of these focus groups was to explore attitudes regarding overall implementation of clinical sequencing in the pediatric setting, the discussions did not specifically address general basic genetic concepts or technical details of genomic sequencing. This lack of an overtly technical, scientific explanation of WES may have contributed to the lack of discussion regarding sensitivity and uncertainty of results in the parent and adolescent groups. Use of hypothetical scenarios to assess opinions and intent to receive results may not accurately reflect decision-making in an actual clinical setting. Finally, comparisons were not made among the represented professional disciplines or diagnostic history of the parent or adolescent participants. A majority of the participants were female and Caucasian, and differences in views between sexes and among individuals from diverse ethnic groups cannot be assessed.

Practice Implications

Based on analysis of these focus group discussions, we have identified discrepancies among professional, parent, and adolescent participants. The following are recommendations for the implementation of pediatric clinical sequencing and are a starting point for more discussion in this area based on findings from an exploratory study.

1. Address genomic sequencing with the patient and family before the scheduled clinic visit during which the family will make a decision about sequencing. Optimally, send home a copy of the consent document or educational materials about sequencing and the potential for incidental findings prior to the appointment.
2. Expect that pre-test informed consent discussions will require additional time outside of the clinic visit to ensure informed discussion of the sequencing test and possible results.
3. Anticipate that families may prefer to have the option on whether or not to include the child in the pre-test discussion of sequencing or in returning results. For parents of adolescents, include where possible the adolescent in the discussion of incidental findings, and facilitate a discussion about WES between parents and children.
4. A strong desire for information about the cause and prognosis of the child's condition may influence the parent's interest in sequencing. Pre-test counseling must therefore include an assessment of the family's understanding of the potential risks of sequencing, the limitations of the test, the availability of incidental findings, and plans for re-interpreting findings in the future. Furthermore, since sequencing is expected to identify the cause of the individual's current condition in about 25% of tests being performed (Eng et al., 2013), clinicians and genetic counselors will need to highlight the possibility of not finding a cause in a majority of cases).
5. Inform parents that results of sequencing may have implications for their own health. For parents who choose not to learn about incidental findings, address under what circumstances, if any, medically actionable results will be returned over the parents' wishes.

Conclusions

The study represents an exploratory assessment of various stakeholders' viewpoints on the implementation of WES in the pediatric clinical setting. By including a variety of professionals-clinicians, bioethicists, genetic counselors, and laboratory directors – as well as parents and adolescents for whom sequencing may be offered in the future, we were able to provide an overview of the differences in concerns and preferences of these groups. In addition, we identified potential discrepancies between professional and patient assessment of the utility of genomic information, which suggests that the views of patients and family members on decision-making will need to be included as guidelines and policies are developed for returning incidental findings from genomic sequencing. Future guidelines for offering WGS and WES in pediatric clinical settings will be informed by findings from research on the preferences of families offered sequencing, provider practices when offering

sequencing and returning results, and the psychosocial and clinical outcomes of testing. Until such data are available, practice will need to be guided by the best interest of the child, skillful counseling about the possible limitations and risks, and ongoing conversation about the lifelong implications of sequencing for both the patient and the family.

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Table I

Demographic Variables of Study Participants (n=49)

Variable	(n)	(%)
Professionals (n=22)		
Gender		
Male	3	14
Female	19	86
Age		
30-39 years	6	27
40-49 years	9	41
50-59 years	5	23
60-69 years	2	9
Race/Ethnicity		
White/Non-Hispanic	21	95
White/Hispanic	1	5
Occupation		
Genetic Counselor	9	41
Physician	6	27
Lab Director	5	23
Bioethicist	2	9
Parents (n= 20)		
Gender		
Male	4	20
Female	16	80
Age		
20-29 years	1	5
30-39 years	3	15
40-49 years	10	50
50-59 years	6	30
Race/Ethnicity[b]		
White/Non-Hispanic	19	95
White/Hispanic	--	--
Education		
High School Diploma	2	10
Some College	4	20
Master’s Degree	8	40
Professional Degree	6	30
Child’s Diagnosis		
Hearing Loss	1	5
Sudden Cardiac Arrest	3	15
Mitochondrial Disease	3	15
Autism Spectrum Disorder	8	40

Variable	(n)	(%)
Multiple Conditions	4	20
Adolescents (n=7)		
Gender		
Male	1	14
Female	6	86
Age		
13-18 years	7	100
Race/Ethnicity[a]		
White/Non-Hispanic	6	86
White/Hispanic	--	--
Diagnosis		
Hearing Loss	3	43
Sudden Cardiac Arrest	4	57

[a]Ethnicity data missing for one participant