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Is Whole Exome Sequencing an Ethically Disruptive Technology? Perspectives of Pediatric Oncologists and Parents of Pediatric Patients with Solid Tumors

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Abstract

Background—Some anticipate that physician and parents will be ill-prepared or unprepared for the clinical introduction of genome sequencing, making it ethically disruptive.

Procedure—As part of the Baylor Advancing Sequencing in Childhood Cancer Care (BASIC3) study, we conducted semi-structured interviews with 16 pediatric oncologists and 40 parents of pediatric patients with cancer prior to the return of sequencing results. We elicited expectations and attitudes concerning the impact of sequencing on clinical decision-making, clinical utility, and treatment expectations from both groups. Using accepted methods of qualitative research to analyze interview transcripts, we completed a thematic analysis to provide inductive insights into their views of sequencing.

Results—Our major findings reveal that neither pediatric oncologists nor parents anticipate sequencing to be an ethically disruptive technology, because they expect to be prepared to integrate sequencing results into their existing approaches to learning and using new clinical information for care. Pediatric oncologists do not expect sequencing results to be more complex

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Contributions: LBM, MJS, ALM, RLS, CME, RAG, DWP, and SEP designed the BASIC3 study, including its Project 3 on the ethical, legal, and social dimensions of WES in pediatric oncology. LBM, MJS, and ALM undertook the qualitative, thematic analysis of the transcripts and prepared the initial drafts of the paper. LBM, MJS, ALM, RLS, DWP, and SEP wrote subsequent, successive drafts of the paper. LBM, MJS, ALM, RLS, CME, RAG, DWP, and SEP prepared and approved the final, submitted version.

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than other diagnostic information and plan simply to incorporate these data into their evidence-based approach to clinical practice although they were concerned about impact on parents. For parents, there is an urgency to protect their child's health and in this context they expect genomic information to better prepare them to participate in decisions about their child's care.

Conclusion—Our data do not support concern that introducing genome sequencing into childhood cancer care will be ethically disruptive, i.e., leave physicians or parents ill-prepared or unprepared to make responsible decisions about patient care.

Keywords

childhood cancers; disruptive technology; qualitative research; whole exome sequencing

Introduction

As whole exome sequencing (WES) and other forms of genomic sequencing are transitioned from research methods to clinical tools, they offer the potential to transform clinical practice by providing an unprecedented scope of genomic information about patients' conditions, disabilities, diseases, disorders, and syndromes.¹⁻³ The care of pediatric patients with cancer typifies the challenges of this important transition. The initial work-up and treatment for childhood cancers is a very stressful process for patient and parents alike. Treatment is highly specialized and largely standardized through the use of evidence-based protocols. In such an urgent and focused clinical context, it has been hypothesized that the scope and complexity of genomic information may become psychosocially burdensome, e.g., by increasing parental anxiety. Secondary or incidental genomic findings have been hypothesized to be particularly challenging.^{4,5} Pediatric oncologists and parents may therefore experience genome sequencing as a disruptive technology.⁶⁻⁹

The concept of a disruptive technology is commonly used in an economic context. "Economically disruptive technologies—like the semiconductor microchip, the Internet, or steam power in the Industrial Revolution—transform the way we live and work, enable new business models, and provide an opening for new players to upset the established order."^{10, p. iii} Genome sequencing appears to be disruptive in all three senses. Emerging companies have created new business models of direct-to-consumer testing. New players in the form of new genome laboratories are creating a competitive market for services. More to the point, sequencing is beginning to transform pediatric oncology by refining the patient's cancer diagnosis and providing unexpected information about new non-cancer diagnoses, risk assessment for cancer and non-cancer diagnoses, reproductive risk assessment, pharmacogenomics, and variants of unknown clinical significance.¹¹ Incorporating into clinical practice such an as-yet unproven, although sophisticated and powerful, technology, has the potential to disrupt the priorities of evidence-based practice. The result could be ethically disruptive: Introducing WES will leave clinicians and parents ill-prepared or unprepared to make responsible decisions about patient care based on WES results.

In the absence of quantitative studies, qualitative research is essential for determining whether those using a potentially disruptive technology expect it also to be ethically disruptive. The clinical setting of pediatric oncology provides an important and timely

research setting to qualitatively study the expectations of clinicians and parents. In this setting, both tumor and germline sequencing data are of potential clinical relevance – to both current and future management of the patient's cancer and to the management of germline results detected in the family. There are no empirical studies that explore the expectations of the oncologists and parents of pediatric patients with cancer regarding genomic sequencing as potentially ethically disruptive, i.e., leaving them ill-prepared or even unprepared to make responsible decisions about patient care. This paper deploys the methods of qualitative research,^{12,13} is to determine whether a sample of pediatric oncologists and parents of children with solid tumors who have entered into a clinical trial of WES report that they expect themselves to be ill-prepared or unprepared to incorporate WES into decision making about the care of children with cancer.

Methods

Baylor Advancing Sequencing in Childhood Cancer Care (BASIC3) Study

The BASIC3 study, a National Human Genome Research Institute and National Cancer Institute-funded Clinical Sequencing Exploratory Research program project, seeks to integrate information from clinical germline and tumor WES into the care of newly diagnosed solid tumor pediatric patients at Texas Children's Cancer Center (TCCC) and evaluate the impact of these exome data on the patients' parents and oncologists.^{14,15} The study was approved by the Baylor College of Medicine Institutional Review Board, which is also the IRB for Texas Children's Hospital, the study clinical site. The study follows pediatric patients with newly diagnosed CNS and non-CNS solid tumors (target enrollment n=280) at TCCC for two years after performing WES of tumor (if available) and blood samples in a CLIA and CAP-certified laboratory. After the resulting germline and tumor WES reports are placed into the electronic health record, the BASIC3 study principal investigators and genetic counselors briefly summarize the results for the patient's primary oncologist and offer to meet to review the reports. The oncologist and a study genetic counselor then disclose the WES results to parents in the pediatric oncology clinic. The potential impact of tumor and germline WES findings on clinical decision-making is assessed through evaluation of the tumor and germline mutations identified, review of the medical record over the two-year follow-up period, and interviews of the pediatric oncologists and patients' parents.

Data Collection

We conducted a longitudinal qualitative study with a cohort of pediatric oncologists (n=16) and a cohort of English-speaking pediatric patients' parents (n=40) participating in the BASIC3 trial for children with a range of cancer diagnoses. (Supplementary Table 1). (Data from Spanish-speaking parents have not yet been analyzed and therefore will be reported separately.) Our research goal was to elicit and describe pediatric oncologists' and pediatric patients' parents' expectations and attitudes concerning the impact of WES on clinical decision-making, clinical utility, and treatment expectations or outcomes. Over the course of the BASIC3 study, the participants in each cohort participate in three semi-structured interviews. The interviews were designed to follow the clinical process of WES sequencing: the first set of interviews is conducted after entry into the study but prior to return of WES

results, the second set following return of WES results, and the third set one year post disclosure. The data presented here are from the first set of these interviews, collected from the start of study enrollment in August 2012 through January 2014.

Pediatric oncologists who care for children with solid tumors (CNS and non-CNS) were recruited from the TCCC and formally consented to participate. As part of the BASIC3 study, they were provided two educational sessions, the first orienting them to both WES and the BASIC3 study design, and the second focusing on the details of WES report formats, for example, interpreting report categories. Following enrollment, their enrollment status and contact information were uploaded into a project-wide database managed by the Baylor College of Medicine Institute for Clinical and Translational Research (ICTR). We extracted and used their email and office phone numbers to schedule the first set of interviews (August 2012-December 2012).

Semi-structured interviews were designed to elicit pediatric oncologists' views concerning the utility of WES technology and results in pediatric oncology care. Topics included treatment impact, oncologist roles, parent involvement, and shared decision-making. Interviews were audio recorded and transcribed verbatim.

A detailed description of parental enrollment procedures has been previously documented.¹⁵ Following consent, their contact information (e.g. phone number) was uploaded to the ICTR database, at which time an automated email was distributed to primary study staff. Upon receipt of this email, we contacted patients' parents by phone to schedule the first set of interviews. Semi-structured interviews were designed to elicit parents' views on participating in the BASIC3 study and their thoughts about the prospect of receiving their child's WES results. Topics included discussions of their child's illness, their decision-making processes, expectations of WES, types of results, and possible benefits and concerns. We conducted these interviews in conjunction with outpatient visits, in-patient admissions, or at times and places convenient for the parents (e.g. their homes). Interviews were audio recorded, and typically lasted between 60 and 90 minutes and involved one parent.

Data Analysis

All interviews were transcribed verbatim by a professional transcription service. Transcripts were reviewed for accuracy and uploaded to ATLAS.ti (v 7.5.1 Scientific Software Development GmbH), a qualitative data management software program.

In qualitative research the natural language statements by participants in transcripts are the data to be analyzed. We analyzed transcripts using thematic analysis¹² to develop a coding scheme and codebook identifying broad and then more specific themes across interviews. We used a deductive approach (themes are extracted from current literature) to formulate initial codes based on research questions, then inductively (themes are based on natural language statements of subjects) identified and structured emergent themes and codes. Research staff and faculty first independently coded each transcript and then met as a group to reach consensus in coding for each transcript.¹³ The interviews did not ask explicitly about whether participants expected WES to be an ethically disruptive technology. This

theme emerged inductively in our analysis and we report quotations that illustrate this theme.

To protect confidentiality, we refer to both pediatric oncologists and patients' parents only with an identification number in brackets after quotations or references attributable to an individual. We have removed potentially identifying information, such as disease-specific expertise or town of residence. As part of the consent process participants were informed that they might be asked to be interviewed. Parents were provided \$25 incentive at the end of each interview. The oncologists received no incentive.

Results

Oncologists' Perspectives

Oncologists' perspectives on whether WES is a disruptive technology were two-fold. On the one hand, they did not perceive it to be ethically disruptive because they regarded themselves as research-driven, evidence-based clinicians. They viewed WES as merely one more data source for evidence-based practice that they were prepared to use. In explaining why WES is not that different from other aspects of clinical practice, one oncologist explained, "I believe in science...I've grown up in an institution that's very much all about evidence-based medicine." [108] They recognized that WES would challenge current evidence-based understanding of pediatric solid tumors and their clinical management, e.g., by providing new information on disease pathways and thus potential treatments [107]. This new information, however, was expected to augment the current fund of knowledge, not replace it.

Oncologists reported that they planned to rely on thorough preparation coupled with an approach of respectfully directive guidance of parents in the disclosure sessions about how to interpret and clinically apply WES results. This approach is not shared decision making, in which such a directive approach is not used. The oncologists in our study reported that they already use this approach with parents in decision making about the clinical management of childhood cancers. As a consequence, in the context of pediatric cancer care, these oncologists expect to report WES results and could counsel parents about clinical implications just as they would other clinically complex information. Taking a research- and evidence-based approach to new technology and information, they expected routine integration of WES into their clinical practice, relating WES to other diagnostic test results. All 16 oncologists took this view, typified by: "I don't really see it as different than my returning other testing information or diagnostic information." [113]

Oncologists anticipated that WES results might be ethically disruptive for parents, however. For example, some oncologists raised concerns that communicating complex findings from WES might disrupt the decision making process for treatment because parents might misinterpret the implications of some findings. [107]. One oncologist explained, "I think I worry a little bit about if it's very complicated, how to explain it to them, or that they'll think, 'Oh, well clearly there's a choice,' or something, and there may be no choice. I mean it may just be information." [111] Another described how these results have the potential to further distract parents from making decisions in the moment about the clinical management of their

child's cancer, "[it] distracts them from what's going on right now...it's sometimes hard to get families to focus on, you know, the present and not worry too much about the future." [109]

The potential psychosocial implications for parents of returning WES results dominated how oncologists think about clinical integration,

"That depends on the results. If it's a clear bill of health, they may be happy. I worry that they might be--you know, say 'oh well, everything's fine. We don't have to worry about anything ever.' And I'm like, 'well, no, hold on.' Some people will want to know and be conscientious of it...Some people will be happy...Some people will be anxious knowing the same information." [114]

They were particularly concerned for those parents who elected to receive carrier status results for recessive disease (the only category of WES results for which parents could opt in or out) as part of their WES reports:

"I'm sure there will be parents who the--the extra information [carrier status results] then becomes more of a burden and a distraction as opposed to a--a means to helping them process the information. Those are the ones I worry most about with this particular study, is that, you know, having the information that isn't relevant to what their child is going through.....And, you know, extra information that isn't related directly to [treatment], you know, processing of all that information I think can be a distraction, as well." [109]

"...the problem is that [carrier status results are] going to induce anxiety. So they might say 'yeah, sure,' then you tell them that they're carrying a recessive gene for some disease and then they might start looking up the disease and worrying about it." [113]

Parents' Perspectives

The dominant theme in our qualitative analysis of the parents' interviews is that they situated their need to be prepared in the context of their experience of their child's diagnosis: many parents reported that they were *blindsided* when their children received a cancer diagnosis. They described wanting to avoid this happening a second time, "if it's going to be something else I have to deal with, I need to know about it and get prepared for it or get him prepared for it, because this blindsided us. This just came out of the blue from nowhere. I never thought we'd ever go through something like this." [308] For our parents, knowing information was more important than not knowing, regardless of potential anxiety: "If there's something bad going on, it's going to be like another little shock, but we would rather know. So a little nervous, but at the same time it's better to know than not to know." [314] Given their children's current medical conditions, and their laser-like focus on saving their children's lives, most parents were not afraid of receiving WES results, much less anxious about doing so.

"I want to save my child. That's the whole point of this. It's like, let's find out more. Let's find out more so we can do a better job. Right? Stop shooting in the dark. Let's just find out what we can. I'm not afraid of knowing. I'm not saying it's

something comfortable, but I'm not going to live my life out of fear because I'm afraid of knowledge. You know? I want to be smarter." [232]

Many parents also described receiving WES results in terms of hoping for a negative finding that would quell fears of recurrence or a second cancer in the child or sibling, "I wouldn't have to worry about it as much. You understand? I wouldn't have to say, "Okay, well, you have a predisposition for this." [283]

Contrary to being ethically disruptive, many parents described their urgent desire to take advantage of this new technology, couching this in terms of doing everything possible to help their children. For example, one parent explained,

"I'd never be able to live with myself if I turned down something like this. And, yeah, sure, you're going to have some anxiety, and, yeah, sure, you're going to learn some things that you may not really want to know. But I just—I couldn't live with myself if we were in the same situation in two years and I had a chance to at least know about it." [335]

They also described taking advantage of this new technology for use in making reproductive decisions. Parents expected this information to enhance their decision making and not interfere with it, as one would expect an ethically disruptive technology to do.

"If it was inherited from me or my husband, then I would say, "Let's not have any more kids," to take a chance of going through this again or putting another child at risk or pain or...it's pretty tough, very expensive, and heartbreaking...I don't really want to experience it again. I definitely want more kids. We have two, but if this is inherited, then we more than likely wouldn't have any more." [314]

"If we're both carriers, if we both have the genes for it, it would have been nice to know way beforehand. Way before we were ever married...not because we wouldn't have kids. We would have still had kids, but we would have been more aware...asking more questions, getting more exams than the usual ones that they do." [233]

We emphasize that, while oncologists expressed concerns about how parents might respond to WES results, parents wanted to be prepared for the future course and management of their child's cancer. Given the gravity of their child's diagnosis, all parents discussed to different degrees that they sought and welcomed all sources of clinical information to help them prepare for decisions about their child's care. This priority was so strong that these parents did not anticipate that WES results to be ethically disruptive. Instead, they expected WES results to be one more potentially useful source of clinical information. Indeed, parents welcomed the prospect of receiving WES results, because parents viewed them as an additional layer of information that might provide insight as to why their child developed cancer, whether or not they were carriers for the type of cancer or another heritable disease, or into potential treatment options in case of tumor recurrence – all domains of information pertinent to decision making about their child's care. Only with respect to obtaining carrier status information did some parents have a lower priority which is consistent with the lack of direct medical action associated with these results.

Discussion

The major finding of this study of the anticipatory attitudes of pediatric oncologists and parents regarding the use of WES is that, for different reasons, neither physicians nor parents perceive WES to be an ethically disruptive technology. Both oncologists and parents expect to be prepared to integrate WES results into their already existing approach to learning and using new clinical information related to patient care, even though they have very different views about the value of these reports. For oncologists, this expectation of ready integration is based on their belief that WES results are no more complex than other clinical information with which they deal on a daily basis and that this information will add to, and eventually strengthen, their evidence-based approach to clinical practice. For parents, their child's illness experience has already blindsided them and has been maximally disruptive. In such a context, new clinical information, despite its complexity and cognitive demands, is not expected to produce additional or unmanageable disruption. Moreover, parents of pediatric patients with cancer are highly committed to protecting their child's life and health; consequently, any new information with the potential to enable them to fulfill this commitment is welcomed and perceived as worth the potential risk of anxiety, despite the concern from some oncologists that these results might be threatening for parents.

Many parents put a great deal of thought into their participation in the BASIC3 study. For them, this technology might provide additional information of clinical relevance to the care of their child or other family members. Parents' stories suggest that having this type of information gives them peace of mind – even if the results do not provide definitive answers to their questions, they feel better knowing they tried. As a consequence, many parents plan to incorporate WES results into their existing decision-making process about the clinical management of their children's cancer.

The strengths of our qualitative study include the large sample sizes of both pediatric oncologists (n=16) and parents (n=40). It is likely that our parents' perspectives differ from those of parents with healthy children, highlighting the need for this type of research to be carried out in a variety of clinical settings and not generalized from a single setting or population. Practicing in a large academic and clinical medical center, our oncologists have the resources to smoothly and confidently integrate WES into clinical care, including a variety of genetics and subspecialty clinics to which patients with germline WES findings can be referred; their perspectives and experiences are likely different from the perspectives and experiences of oncologists working in smaller practices or less amply resourced facilities or of physicians in other specialties.¹⁶

Conclusion

In this study, neither the pediatric oncologists nor the parents of pediatric solid tumor patients expect WES to be ethically disruptive. Their reported approaches are expected to transform this potentially ethically disruptive technology into an ethically non-disruptive technology. The oncologists anticipate making WES merely one more component of a comprehensive, seamlessly integrated approach to professionally responsible pediatric cancer care. Parents anticipate placing a paramount value on all of the information that they can obtain about

their children's cancer, including WES results. In the context of the child's illness experience, parents expect WES results to be just one more category of useful information that may help them to cope better with their child's illness and its clinical management. Importantly, our data do not support concern that providing WES results to parents of seriously ill children should be expected to disrupt or undermine parents' preparation to participate in responsible decision making about their child's subsequent clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BASIC3	Baylor Advancing Sequencing in Childhood Cancer Care
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
ICTR	Baylor College of Medicine Institute for Clinical and Translational Research
TCCC	Texas Children's Cancer Center
WES	whole exome sequencing

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