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The Development of a Preference-Setting Model for the Return of Individual Genomic Research Results

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Abstract

Understanding participants' preferences for the return of individual research results (IRR) in genomic research may allow for the implementation of more beneficial result disclosure methods. We tested four preference-setting models through cognitive interviews of parents to explore how parents conceptualize the process of setting preferences and which disease characteristics they believe to be most important when deciding what results to receive on their child. Severity and preventability of a condition were highly influential in decision making and certain groups of research results were anticipated by participants to have negative psychological effects. These findings informed the development of an educational tool and preference-setting model that can be scaled for use in the return of IRR from large biobank studies.

Keywords

pediatrics, genomic research, individual research results, participant preferences, biobank, return of results, cognitive interviews, qualitative research, pediatrics

The issues surrounding whether or not to return individual research results (IRRs), and the role of participant preference in the process, has been an area of controversy, particularly as whole genome/exome sequencing has become increasingly available and affordable. There is some consensus around criteria for the return of IRRs among experts based on analytical validity, health implications for the participant, and clinical actionability (Bookman et al., 2006; Fabsitz et al., 2010; Gutmann et al., 2013; Wolf et al., 2012). Some have suggested that a finding *may* be disclosed to a participant: when it is not actionable but may be deemed important by the participant (Wolf et al., 2008), or when the potential benefits outweigh the risks of disclosure (Bookman et al., 2006; Fabsitz et al., 2010). In part due to the complexity of returning results and the gray area in these recommendations, only 18% of the 73 U.S. research biobanks sampled in 2012 were returning results "of some sort" to participants (Wolf, 2012). The Presidential Commission for the Study of Bioethical Issues proposed that researchers do *not* have a duty to disclose IRRs to study participants but should have a clear plan, and that if IRRs are offered, participants should have the option to opt out (Gutmann et al., 2013). Jarvik et al. (2014) echoed these recommendations.

The principles of beneficence, non-maleficence, and reciprocity apply to research as well as to clinical care (Shalowitz & Miller, 2005). In genomic research, participant benefit can be maximized by taking into account participant preferences for return of results, and by disclosing IRRs that include, but are not limited to, those that are clinically actionable (Ravitsky & Wilfond, 2006). This approach is grounded in the view that participants have a moral claim to result disclosure and emphasizes the "personal utility" (Foster, Mulvihill, & Sharp, 2009; Grosse, Kalman, & Khoury, 2010; Grosse, McBride, Evans, & Khoury, 2009; Khoury et al., 2009) and personal meaning (Kohane & Taylor, 2010; Ravitsky & Wilfond, 2006; Rothstein, 2006) of the genomic information, and recognizes that participant priorities may not be directly aligned with what is "medically actionable." In fact, when subject preferences are truly taken into account, the criteria for return expands beyond what is "medically actionable" to "personal utility," ranging from satisfying curiosity, to allaying anxiety, to communication with other family

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members, to purchasing insurance. The Informed Cohort model (Kohane et al., 2007) is one approach to the return of genomic research results that maximizes benefit by allowing participants to exercise their autonomy by designating their preferences for which research results to receive, while protecting them from harm through ethical oversight of the results returned by the Informed Cohort Oversight Board (ICOB; Holm et al., 2014; Holm & Taylor, 2012). The Coriell Personalized Medicine Initiative has implemented this model (Kronenthal, Delaney, & Christman, 2012), and Boston Children's Hospital (BCH) is working toward implementing this model in a pediatric biorepository, termed *Gene Partnership*.

There are challenges in designing a preferences-based results return process for genomic biobank research. The method has to allow participants to exert their preferences with some degree of granularity, yet be feasible for large-scale genomic repositories. In addition, participants may not truly understand the implications of their choice of research results to receive. In a focus group study exploring the attitudes of parents toward the receipt of IRRs on their child (Harris et al., 2012), although many parents initially express a desire to learn about all findings relevant to their child's health, when probed to consider results including for severe, untreatable diseases, and results that are not well established, many parents fine-tune their preferences to a more limited scope of results, citing anxiety or psychological burden (Harris et al., 2012). In a large survey of parents (Ziniel et al., 2014), we saw a similar trend; although initially the majority of respondents (88.7%) desired all results about their child, later in the survey, when faced with questions about results that were severe, non-preventable, untreatable, or not well established, many parents no longer wanted all results (Ziniel et al., 2014).

Finally, current guidelines regarding the return of IRRs in accordance with participant preferences reflect the knowledge of experts and a well-developed canon of research ethics. Few studies address what attributes of IRR participants think are important when they are deciding what IRR they want to receive. In one focus group study (Bollinger, Scott, Dvoskin, & Kaufman, 2012), participants cited potential health benefits and personal reasons for wanting to receive research results, but placed less importance on the degree of the risk and actionability of the result. Several studies have explored patient preferences for the return of incidental findings from genome sequencing in the clinical setting: Bennette et al. (2013) found that the treatability, severity, and lifetime risk of the disease were important considerations, and in a focus group study, Townsend et al. (2012) found that autonomy and patients' rights to choose were important to patients.

Thus, the objective of the preliminary study presented here was to further explore trends in parental preferences for results to develop a preference-setting model that will be tested in a large cohort of parents. Parental preferences were elicited through semi-structured interviews to build a comprehensive patient-centered preference-setting model. While we anticipated that this model would incorporate factors that have been proposed in existing result return guidelines, such as clinical significance, disease severity, imminence and actionability, we also aimed to create a model that was responsive to parents' personal needs and priorities.

Method

We conducted a series of semi-structured interviews with parents designed to investigate (a) how parents conceptualize the process of preference setting, and (b) the specific and personal reasons behind parents' preferences. Because the goal of this study was to construct a well-developed model, we directly incorporated parents' feedback into subsequent models, utilizing an iterative process of testing and adaptation. Emphasis was placed on assessing and enhancing the clarity of the model and the extent to which it allowed parents to successfully articulate their preferences.

Recruitment Methods

A convenience sample of English-speaking parents with a child <18 years of age who was an inpatient in the Medicine Intensive Care Unit (MICU) or Intermediate Care Program (ICP) at BCH were eligible for this study. Participants were enrolled until saturation was reached for each model (until new themes stop emerging); (Glaser & Strauss, 1967; Strauss & Corbin, 1998). The study was approved by the BCH Institutional Review Board and written informed consent was obtained from all participants.

Educational Tutorial

We developed a 7-minute educational video tutorial to provide participants with a basic understanding of genetic health risk and inheritance. The tutorial included information about the nature of open-ended biobank research and the potential value and limitations of research-derived individual results. Feedback from parents in early interviews was used to improve the clarity and effectiveness of the tutorial.

Interview Process

Semi-structured interviews were conducted in patient care rooms or private conference rooms by a genetic counselor or research assistant. Each interview was audio-recorded and lasted approximately 30 to 60 min. Participants were compensated with a US$30 Visa gift card and BCH parking voucher. Each interview began with collection of

demographic information and a viewing of the educational tutorial, followed by an explanation of the hypothetical nature of the biobank exercise. Interviewers then guided parents through the preference-setting model, urging parents to narrate their thought processes while making decisions regarding the types of genetic research results they would and would not want to receive if their child were hypothetically enrolled in a biobank.

Preference-Setting Models

The goal of the study was to develop a preference-setting model that would allow parents to express their preferences for IRR to receive from genetic research, and that they estimated would provide them with the most benefit and cause the least harm. More specifically, our model aimed to

a) be clear and easy to navigate online to accommodate the increasingly large number of study participants involved in research biobanks;
b) encourage parents to consider the various implications of a genetic research result without biasing their preference selection; and
c) capture important subjective aspects of parental preferences in a way that could be scaled for biobanks with large volumes of participant data.

Utilizing an iterative process, four consecutive models were piloted during this study, each designed based on participants' comments, responses, and feedback from the previous model:

1. *Branching diagram model* (Figure 1): A series of branching diagrams that categorized results according to age of onset, preventability, treatability, and severity.
2. *Example-based model* (Figure 2): An example-based approach that allowed parents to freely explain their preference choices based on examples of specific, hypothetical results representing a variety of categories.
3. *Grid model with checklist* (Figure 3): A 2 × 2 decision grid with severity and preventability axes and the opportunity to opt out of certain categories of results based on the affected organ systems.
4. *Step-wise grid model* (Figure 4): A step-wise presentation of the same 2 × 2 decision grid and the opportunity to opt out of four "sensitive" categories of results.

After participants set their preferences, they were provided with examples of hypothetical results they could receive from a biobank based on the preferences they set. In Models 3 and 4, this came in the form of a "hypothetical result report" grid containing 40 examples of conditions that would or would not be disclosed to them based on their choices (see Figure 5). Input from 12 genetic counselors and 8 geneticists at BCH and other Boston area hospitals (including Brigham and Women's Hospital and Beth Israel Deaconess Medical Center) was used to categorize each of the 40 examples as either preventable or non-preventable and either severe or non-severe. Conditions were only included in the model if a majority of respondents (>55%) agreed on categorization. Nearly all conditions reached 65% concordance (and many well over 89%); hypothyroidism and generalized anxiety disorder were only agreed upon by 55%.

Results

Participants

A total of 25 parents participated in this study (Table 1). Six parents declined participation. Reasons for declining were that they were distracted by their child's medical condition or they felt they did not have the time. For each model, we interviewed parents until we reached saturation; 3 parents were interviewed for Model 1, 4 for Model 2, 4 for Model 3, and 14 for Model 4. The age range was 27 to 53 years with a mean of 39 years.

Results Regarding Model Development

Model 1: Branching diagram model. We developed two versions of our first preference-setting model, one for adult-onset and the other for childhood-onset conditions (Figure 1). Each "branch-point" dichotomized potential results based on characteristics of health conditions deemed important in existing studies (Fabsitz et al., 2010; Harris et al., 2012): possible interventions (prevention, treatment, personal utility) and level of severity (from mild or minimal discomfort to fatal or disabling). For each of these characteristics, a basic definition was provided and parents were asked to decide whether or not they would want to receive those types of results. We differentiated between interventions that prevented the disease from occurring (preventing onset), changing the course of the disease, and just treat the symptoms. Parents were subsequently presented with two sets of hypothetical results: those that they might and those they might not receive based on their stated preferences. Parents were then asked to elaborate on whether those results were consistent with the preferences.

Parents found the structured format confusing and it did not reflect what parents thought about the attributes of the results. The branching diagram required that parents consider each new dimension or "branch" in light of the previous one and the dimensions were prioritized in a way that did not always resonate with them.

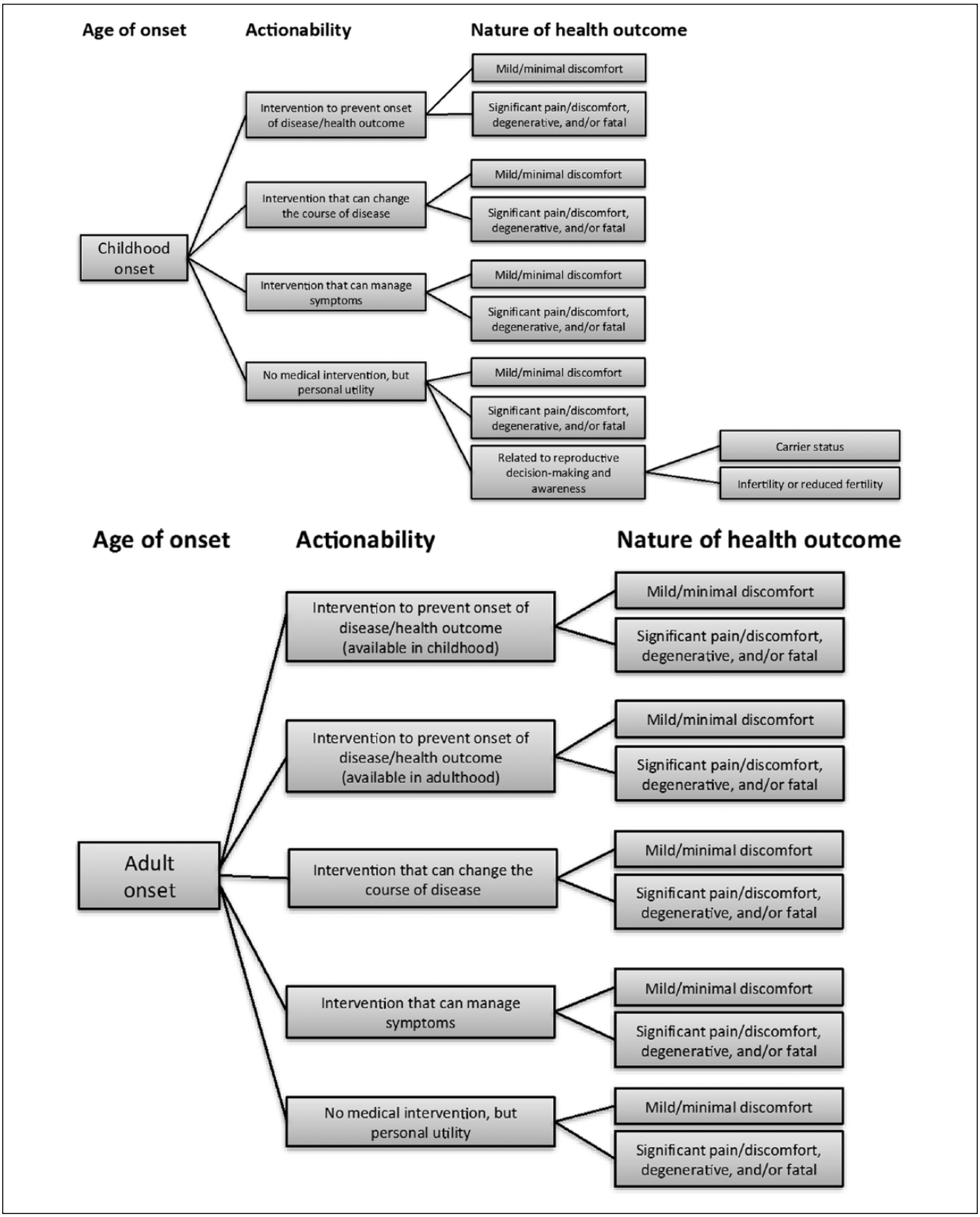

Figure 1. Branching diagram models for childhood-onset and adult-onset conditions.

Participant ID:	**Child's diagnosis:**	**Date:**
Condition	**Result wanted (Y/N)?**	**Explanation**
1. Juvenile diabetes	*Yes*	*Reasons...*
2. Scoliosis		
3. Dementia		
4. Food allergy		
5. Melanoma		
6. Alcoholism		
7. Coumadin sensitivity		
8. Rheumatoid arthritis		
9. Dyslexia		
10. Ovarian cysts - PCOS		
11. Breast cancer		
12. Poor vision/astigmatism		
13. Hypothyroidism		
14. Autism		
15. Cataracts		
16. Alopecia		
17. Type 2 diabetes		
18. ALS		
19. Iron deficiency anemia		
20. Obesity		
21. Juvenile rheumatoid arthritis		
22. FAP colon cancer		
23. Anxiety		
24. Vitiligo		
25. Environmental allergies		
26. Celiac disease		
27. Cystic Fibrosis carrier		
28. Fragile X carrier		
29. Increased susceptibility to meningitis (properdin deficiency)		
30. ADHD		
31. Huntington's disease		
32. Kidney stones		

Figure 2. Example-based model.

Model 2: Example-based method. For Model 2, we discarded the predetermined categories and hierarchies of Model 1 and instead explored how parents prioritize disease characteristics in a more organic and open-ended way. Parents were shown 32 hypothetical examples of health conditions for which they could theoretically receive results (Figure 2), accompanied by a brief "glossary" written by geneticists and genetic counselors describing those conditions. Parents

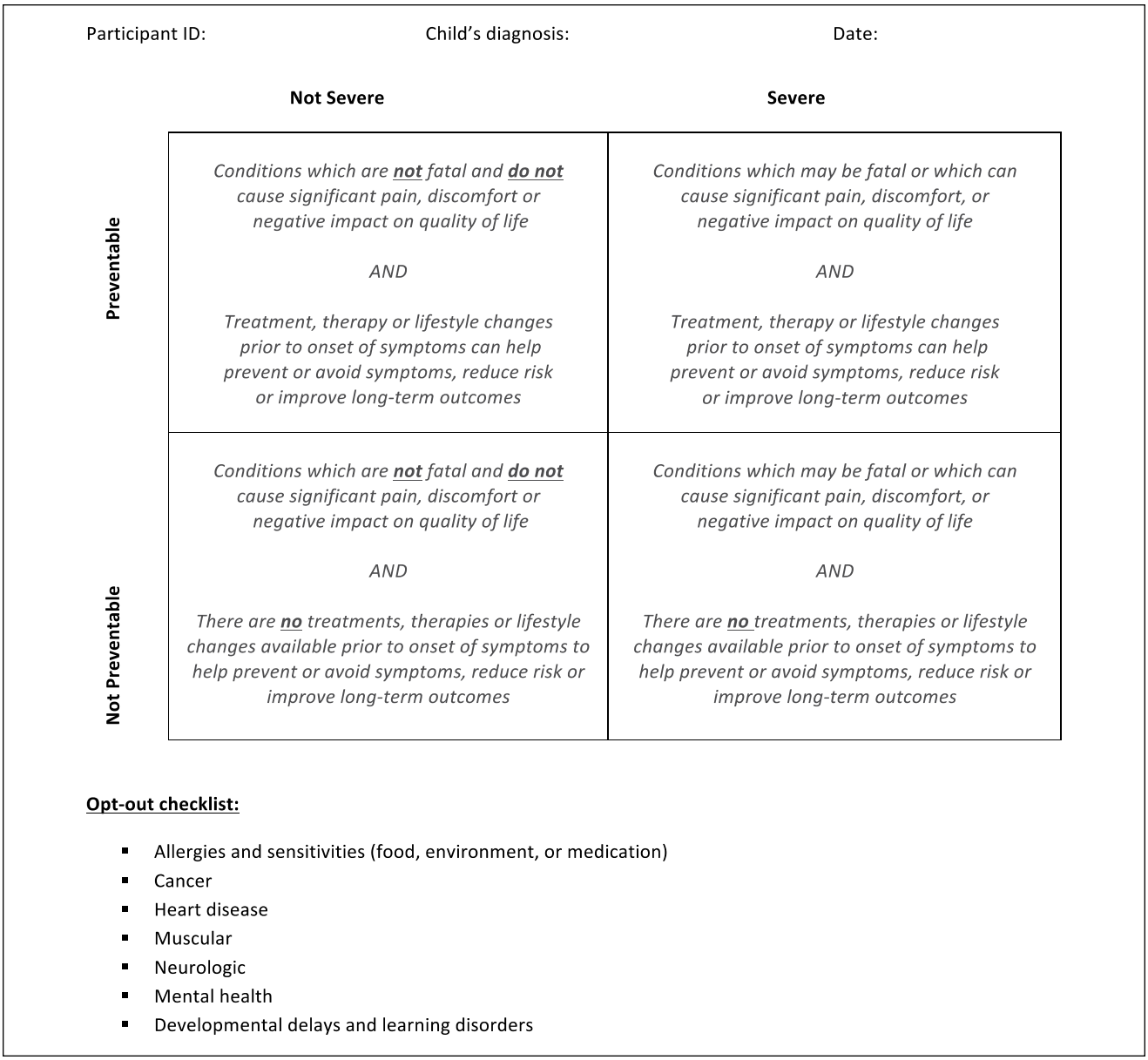

Figure 3. Grid model with opt-out checklist.

were asked to talk us through their thought processes for deciding which results they would or would not want to receive, and to articulate the criteria and constructs they used when deciding whether or not they would want a particular result to be returned.

Two dimensions from the branching diagram model emerged as the most important in discriminating what types of results parents wanted: preventability and severity. First, not only did parents distinguish between diseases which could be prevented through interventions initiated before the onset versus diseases that could be treated after the onset, that is, between pre-symptomatic prevention versus post-symptomatic treatment, but also when deciding what results to receive, whether a condition was preventable or non-preventable was the important factor; some parents desired both preventable and non-preventable conditions while others desired only preventable conditions. The second important factor was the extent to which a given condition would affect their child's quality of life. Some parents wanted to only hear about severe conditions, whereas others wanted to hear about condition regardless of severity.

As a result, we constructed our next preference-setting model around a framework that gave parents an opportunity to define which results to receive based on the two dimensions—severity and preventability. We also decided to explore the possibility that parents may have preferences

Q1. Preventability: Preventable conditions are those for which, prior to onset of symptoms, there is some treatment, therapy or lifestyle change that can be made to help prevent or avoid symptoms, or reduce risk. What types of results would you like to receive about your child based on this description of preventability?

- ❑ Preventable conditions only
- ❑ Non-preventable conditions only
- ❑ Both preventable & non-preventable conditions
- ❑ Neither

Q2. Severity: Severe conditions are those which may be fatal or which can cause significant pain, discomfort or negative impact on quality of life. Given what you previously said about preventability, what types of results would you like to receive about your child based on this description of severity?

- ❑ Severe conditions only
- ❑ Not severe conditions only
- ❑ Both severe & not severe conditions
- ❑ Neither

Not severe & non-preventable conditions These conditions are NOT fatal and do NOT cause significant pain or discomfort. The symptoms of these conditions CAN NOT be prevented or avoided prior to onset.	**Severe & non-preventable conditions** These conditions are fatal and/or cause significant pain or discomfort. The symptoms of these conditions CAN NOT be prevented or avoided prior to onset.
Not severe & preventable conditions These conditions are NOT fatal and do NOT cause significant pain or discomfort. The symptoms of these conditions CAN be prevented or avoided prior to onset.	**Severe & preventable conditions** These conditions are fatal and/or cause significant pain or discomfort. The symptoms of these conditions CAN be prevented or avoided prior to onset.

Q3. Would you like to EXCLUDE results about your child regarding any of the following categories?

i.) Mental illness and psychological conditions (e.g. substance abuse, depression, schizophrenia)?

- ❑ Yes, I would like to EXCLUDE these results
- ❑ No, do not exclude

ii.) Developmental disorders and learning disabilities (e.g. mental retardation, ADHD, dyslexia)?

- ❑ Yes, I would like to EXCLUDE these results
- ❑ No, do not exclude

iii.) Degenerative neurological conditions (these conditions cause progressive deterioration of the brain and nervous system)?

- ❑ Yes, I would like to EXCLUDE these results
- ❑ No, do not exclude

iv.) Adult-onset conditions for which there is no prevention or intervention during childhood (e.g. Huntington's disease, Alzheimer's disease)?

- ❑ Yes, I would like to EXCLUDE these results
- ❑ No, do not exclude

Figure 4. Step-wise grid model.

around categories of diseases and want to opt out of results for certain diseases categories.

Model 3: Grid model with checklist. In the third approach to preference setting, parents were shown a grid (Figure 3) dividing hypothetical research results into four categories according to the following definitions of preventability and severity: "Preventable conditions are those for which, prior to onset of symptoms, there is some treatment, therapy or lifestyle change that can be made to help prevent or avoid symptoms, or reduce risk," and "Severe conditions are those which may be fatal or which can cause significant pain, discomfort, or negative impact on quality of life." Parents were asked to identify which of the four "boxes" of result types they would or would not want to receive: non-severe and preventable, non-severe and non-preventable, severe and preventable, and/or severe and non-preventable. We also provided a separate checklist of disease categories (including allergies and sensitivities, cancer, heart disease, muscular conditions, neurologic conditions, mental health conditions, and developmental delays) and asked parents if they wanted to opt out of any of these categories.

Not severe & non-preventable	Severe & non-preventable
1. Attention deficit hyperactivity disorder [a] 2. Essential tremor 3. Generalized anxiety [a] 4. Hypothyroidism 5. Poor vision 6. Seasonal allergies 7. Turner Syndrome 8. Vitiligo 9. Mitral valve prolapse 10. Obstructive sleep apnea	1. Autism [a] 2. Bipolar disorder [a] 3. Duchenne Muscular Dystrophy 4. Juvenile (Type I) Diabetes 5. Juvenile rheumatoid arthritis 6. Polycystic Ovarian Syndrome 7. Rett Syndrome [a] 8. Acute lymphoblastic leukemia 9. Batten disease (NCL) [a] 10. Alzheimer's disease [a] 11. Huntington's disease [a]
Not severe & preventable	**Severe & preventable**
1. Pet dander (dog) allergy 2. Iron deficiency anemia 3. Kidney stones 4. Lactose intolerance 5. Gastroesophageal reflux disease 6. Reduced response to ibuprofen 7. Chronic mild constipation 8. Delayed response to local anesthetic 9. Increased susceptibility to cavities	1. Alcoholism [a] 2. Asthma 3. Deep vein thrombosis 4. Familial hypercholesterolemia 5. Melanoma 6. Peanut allergy 7. Types II Diabetes 8. Malignant hyperthermia 9. Childhood onset hereditary colon cancer 10. Aortic aneurism

Figure 5. Conditions on the hypothetical result report in each category.
Note. Opt-out categories and conditions:
Mental health and psychological conditions: alcoholism, generalized anxiety, bipolar disorder
Developmental disorders and learning disabilities: attention deficit hyperactivity disorder, autism
Childhood-onset degenerative disorders: Rett syndrome, Batten disease (NCL)
Adult-onset non-preventable: Alzheimer's disease, Huntington's disease
[a]Indicates a condition included in the opt-out categories.

The concrete definitions of severity and preventability seemed to be more readily understood by parents than those of the previous model as evidenced by higher concordance between stated preferences and satisfaction with hypothetical results returned. Still, many parents felt that the model was cluttered and would be difficult to navigate online.

No parent opted out of receiving an organ-system category of diseases. However, strong reactions were observed when parents were prompted to consider mental illnesses, developmental conditions, and adult-onset conditions. Nearly every parent said they would decline results regarding at least one of the following conditions: attention deficit hyperactivity disorder, dyslexia, alcoholism, or amyotrophic lateral sclerosis. The complex or stigmatizing nature of these conditions were cited by parents who did and did not want those results.

Thus, for the next model we gave parents the opportunity to exclude certain categories of diseases that might make them uncomfortable. In addition, based on occasional confusion with the presentation of the grid in Model 3, we decided that a step-wise approach should be taken in Model 4.

Model 4: Step-wise grid model. In the step-wise process of Model 4 (Figure 4), parents were given an overview of the process so that they knew what to expect. Parents were then asked to set their preferences first regarding preventability and second regarding severity. Finally, parents were given the opportunity to opt out of results regarding (a) mental illnesses and psychological conditions, (b) developmental disorders and learning disabilities, and/or (c) childhood-onset degenerative neurological conditions.

Concordance between parents' stated preferences and the results they received based on those preferences was highest for this model. Parents generally felt the model was clear, and that it was easy to set their preferences following a step-wise process. One mother however repeatedly expressed her desire to receive only the "dreaded diseases"—those fatal, untreatable diseases which would

Table 1. Demographic Characteristics of Participants.

	n	%
Gender		
Male	4	16
Female	21	84
Race		
Caucasian	19	76
African American	4	16
Asian	1	4
Declined	1	4
Ethnicity		
Hispanic	4	16
Non-Hispanic	21	84
Highest level of education		
High school or equivalent	3	12
Some college/vocational school	3	12
2 or 4-year college degree	11	44
Postgraduate courses/degree	8	32
Previous research participation (participant or child)	13	52
Previous genetic testing (participant or child)	12	48
Diagnosed with genetic disorder (participant or child)	11	44

cause "unbearable" psychological suffering—providing the example of amyotrophic lateral sclerosis. This poignant remark led us to amend our opt-out list to include a fourth category: adult-onset conditions with no interventions during childhood. As the existing clinical recommendations from the American College of Medical Genetics (ACMG; Green et al., 2013) include both childhood-onset and adult-onset conditions, we also introduced the final options as a way to clarify the relevance of age of onset.

Results Regarding Parental Preferences

Based on statements from the parents, we applied the criteria of preventability and severity used in Models 3 and 4 to the participant data from the first two models. Table 2 shows the distribution of preferences in our group of parents.

Preventability. All parents interviewed said they would want to receive results about preventable conditions. More than half of these parents ($n = 16$, 64%) desired research results regarding both preventable and non-preventable conditions, while the remaining parents ($n = 9$, 36%) wanted to receive preventable conditions only. Notably, no parent elected to receive only results regarding non-preventable conditions. Parents felt they would be empowered by all results, citing a broader definition of "clinical utility" that included the possibility of avoiding a diagnostic odyssey. Parents said they would appreciate the chance to take any action that might "combat the increased risk," citing the benefits of preventive therapies, behavioral interventions, and lifestyle changes.

Table 2. Preference Results.

Results desired	*n*	%
Preventability of condition		
Preventable conditions only	9	36
Non-preventable conditions only	0	0
Both preventable and non-preventable conditions	16	64
Severity of condition		
Severe conditions only	4	16
Non-severe conditions only	2	8
Both severe and non-severe conditions	19	76

Parents who set their preferences to receive *only* preventable conditions (refusing non-preventable) commonly cited a desire to avoid unnecessary or unproductive anxiety. For many, the inability to take action would make "the psychological impact of knowing about it worse than any benefit." Similarly, another mother noted, "I think it would actually take more of a mental toll on you, with the 'what ifs.' And I think sometimes you don't need the 'what ifs.'" One parent believed that if there was nothing she could do for her child before the onset of symptoms, her wish would be to "protect that time of innocence" as much as possible.

Parents who wanted to receive both preventable and non-preventable results cited prior uncertainty with a child's medical condition and the feeling of empowerment afforded by more information as primary motivating factors. Rather than highlighting the uncertainty associated with many genetic results, parents with this "knowledge is power" attitude emphasized the possible benefits of symptom recognition and early detection, regardless of whether or not they would choose to share those results with their physician. Many parents also said that they would be grateful for the opportunity to mentally prepare themselves and their children for a potential future diagnosis. "To have that foresight, helps you make better choices about life," said one father, referring to housing, finances, and insurance.

Severity. The majority of parents ($n = 19$, 76%) wanted to receive both severe and non-severe conditions, while the remaining six parents wanted either severe conditions only ($n = 4$, 16%) or non-severe conditions only ($n = 2$, 8%). Parents who elected to receive only non-severe conditions often cited a desire to avoid the psychological burden of "scary" conditions, adding comments such as, "I tend to be more of a 'worst case scenario' person." These parents felt that the anxiety associated with the inherent uncertainty of research results would be amplified in the case of more severe conditions. A small number of parents declined severe results because they believe those results would alter their expectations of, or relationship with, their child. One mother said, "If you think 'oh my god, she's going to have cancer when she's older,' then you're going to treat them differently."

Other parents chose to decline non-severe conditions and receive only "results limited to things that may affect quality of life and life span." Even though parents understood that many of these severe conditions are untreatable, they felt that these findings would help them to mentally prepare. These parents believe that milder conditions are simply a part of life, and that worrying about—or even learning about—a predisposition for such a condition would be counterproductive. One mother felt that she would want to know only the more serious predispositions in advance, so that she could establish a strong "network and all the care providers" and relocate near family or treatment facilities if necessary

The majority of parents, however, expressed interest in receiving results regarding both severe and non-severe conditions. These parents were often non-selective with respect to results: "I want everything. I want to know and then I want to *know* know" said one mother; "I'm just curious. I want to know everything about anything there is to know," responded another. Some of these parents felt that there was no real downside to having more knowledge about their child's health, while others acknowledged the potential psychological consequences but said that they would welcome the information regardless.

Generally, previous experience with a child's significant health issue seemed to have a great influence on a parent's preference with regard to severity. Parents who were in the intensive care unit for a first-time diagnosis or first-time allergy attack, for example, were more sensitive and reactive to the severe hypothetical conditions, and set their preferences to receive non-severe conditions only. These parents had limited experience with—and thus limited tolerance for—the uncertainty or anxiety associated with many severe conditions. On the other hand, parents of children admitted to the hospital for chronic or genetic conditions often had a higher threshold for what they considered "severe." This sentiment was illustrated by one woman's comment, "Once you have been told that your child is likely going to die, I don't think there is any worse information you could possibly tell me. So bring it on."

Opt-Out Categories

Of the 14 parents, 2 declined the possibility of learning about psychiatric conditions, 2 opted out of developmental conditions, and 3 out of degenerative conditions. We added the option to opt out of receiving adult-onset conditions on their child for only 4 of the interviews, and none of the 4 parents opted out of receiving results for adult-onset conditions on their child.

Familiarity with a disease. Familiarity was often a primary reason for both wanting and not wanting a result, as parents generally reacted strongly to conditions for which there was a family history. Many parents welcomed the additional information because it would encourage them watch for symptoms or make lifestyle modifications. Conversely, some parents felt that this information would be superfluous or even harmful. One mother said, "You don't need genetic testing to tell you that [your child is predisposed] if three of your grandparents are alcoholics."

Autonomy. Parents were divided on the issue of being the recipient of a child's genetic result. Some parents wanted to receive results on their child as they felt a parental obligation to have the information and to have the option of delivering the news to their child when their child becomes able to handle it, cognitively and emotionally. For example one parent stated, "At some point, my kids are going to turn from kids to adults and then they have the right to know everything." Others felt that it was important to protect their child's autonomy and decline certain results such as carrier status, adult-onset conditions, and conditions that could potentially affect fertility. As one father stated, "just because I want to know doesn't mean she wants to know."

Previous experience with genetic testing. Previous experience with genetic testing and/or genetic conditions appeared to influence the way parents navigated the preference model. Many who were less familiar with genetic testing needed to talk themselves through the preference-setting exercise, considering the implications of each decision. These individuals benefitted from the grid structure because it allowed them to see the bigger picture and understand how the different criteria overlapped with one another. Parents who had previously contemplated genetic testing, or who were able to readily identify the way they tolerate uncertainty, made decisions more quickly. These individuals often labeled themselves—for example, as a "knowledge is power" person, a "worst case scenario" person, or an "ignorance is bliss" person—and were able to apply that self-awareness to the hypothetical biobank.

Characteristics of the research results itself—Risk and clinical validity. Throughout the interviews, we found that characteristics of a research result itself (i.e., the degree of risk conferred and the extent to which it is well established in the scientific community) did not have as strong an influence as did characteristics of diseases (i.e., preventability and severity). Many parents said that as long as information about risk was included in a result report, the degree of risk conferred by the finding would not affect their decision to receive the result. Some parents in fact seemed unable to conceptualize accurately the actual degree of risk, and thus the degree of risk reported was meaningless to them: "Until you tell me there's no risk at all," one mother said, "in my book, it's still 50/50." Similarly, in nearly every instance, a parent's desire to receive a particular result was not swayed by whether or not that finding was scientifically well established.

Discussion

Recent recommendations on return of research results have emphasized (a) there is no obligation on the researcher to return research results, and (b) that if a researcher offers return of IRR, participants should be given a choice to receive, or not, results (Gutmann et al., 2013; Jarvik et al., 2014). Incorporating more nuance preferences into the return of IRRs, as opposed to an opt-in/opt-out option, may further enhance the benefits for participants by allowing participants to express their desires, and allow them to receive a broader set of results that are not just "actionable" but also have personal utility for them. However, little is known about preferences in terms of which criteria do and do not resonate with participants, which factors are most important when considering receiving IRRs, and how participants personally weigh the harms and benefits of various types of IRRs. The purpose of this preliminary study was to address how participants conceptualize their preferences for return of research results. In this study, we found two primary characteristics that determined whether or not a parent wished to receive a particular result: (a) whether or not there were preventive measures (treatment, intervention, or lifestyle changes that could be made *prior* to the onset of disease to prevent symptoms or improve outcomes), and (b) whether or not the condition could be fatal or would significantly affect quality of life through pain or discomfort.

A most notable finding of our study related to the concept of what parents consider "actionable" when considered what results to receive. Actionability is defined by Knoppers, Deschenes, Zawati, & Tasse (2013) as "a recognized therapeutic or preventive intervention or other available actions that have the potential to change the clinical course of a disease or condition (p. 246)," and was an important factor in the development of the ACMG clinical guidelines (Green et al., 2013) and as the basis for other results "bins" (Berg, Khoury, & Evans, 2011). The first finding regarding actionability was that parents make a distinction in two aspects of actionability, that is, "treatable" and "preventability." Whether or not a condition was treatable was less important to them than whether or not it was preventable. Parents who declined to receive results for non-preventable conditions and only desired results for preventable conditions expressed that they only wanted to hear about condition that they could do something about prior to the onset of symptoms; therefore, whether or not the condition was treatable was not a deciding factor. The other finding regarding actionability was that when parents discussed their understanding of what makes a result "actionable," their definitions went beyond traditional aspects of treatment, such as medical interventions and lifestyle modifications. They emphasized other meaningful interventions such as education, mental preparation, and planning in terms of insurance, housing, and finances, consistent with findings in other research such as the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study (Chao et al., 2008; Gooding et al., 2006; Green et al., 2009; Roberts et al., 2005).

We also found that of the categories of diseases that we presented to parents (cancer, cardiovascular disease, diabetes, etc.), parents had strong responses, both in favor of disclosing and of withholding, to results related to mental illnesses, developmental and learning delays, degenerative conditions, and adult-onset conditions. Some of our participants were unwilling to learn results about these disorders because they could be stigmatizing or could carry a high psychological burden. As a result, we concluded that it was important in our preference model to allow a separate "opt-out" option for these conditions.

Interestingly, characteristics of a research result itself (i.e., the degree of risk conferred and the extent to which it is well established in the scientific community) did not seem to matter much as parents considered results to receive. For many parents, the degree of risk conferred by the finding did not affect their decision to receive the result and others had difficulty understanding what the degree of risk meant. In addition, the finding that some people consider poorly established associations to be just as meaningful as well-established findings suggests that the fully libertarian position that all results should be released to anyone who wants it may in fact be dangerous as the results may be misinterpreted as well established, when in fact they are highly speculative. These findings were similar to the findings of Bollinger et al. (2012) in their focus group study.

Overall as we talked to parents, we identified several common themes in the way that parents navigated the preference-setting model, despite a wide range in motivating factors underlying their decisions, and we could broadly divide parents into categories. Some parents seemed to be "information seekers," who desired all possible results. Some parents seemed to be "action takers," desiring only preventable conditions. And some parents were "worry avoiders," refusing severe conditions. Similar findings were reported in our previous work (Ziniel et al., 2014) in which we used cluster analysis to identify distinct subgroups of respondents based on their responses to questions regarding the treatability, preventability and severity of various types of IRRs.

There is at least one other approach to preference setting in genomic research. Investigators at the University of Washington have developed a web-based tool "My46" (https://www.my46.org/), a self-guided online platform allows participants to opt in to receiving certain categories of sequencing results including disease risk (further broken down by the organ system affected), carrier status, medication response, newborn screening conditions, metabolic disorders, and conditions included in the 2013 ACMG guidelines (Yu, Jamal, Tabor, & Bamshad, 2013). Our model differs in that it does not rely on categories of diseases, as we found the category of disease by organ system

was less important to parents when it came to return of results. Instead, attributes of the diseases, preventability, and severity were the characteristics that mattered most to parents. The only exceptions were mental illnesses, developmental and learning delays, degenerative conditions, and adult-onset conditions for which parents did have strong feelings about receiving results.

There are several limitations to our study. This was a pilot study and the participants were more highly educated than the general population. In addition, the categorization of conditions into one of the four categories is somewhat arbitrary. We had input from genetics specialists to categorize the conditions, but some of the conditions, particularly those in the optional opt-out categories, could be viewed in several different categories. For example, Huntington disease is severe and non-preventable category, a degenerative neurological conditions category, and an adult-onset condition. This overlap of categories could affect how participants view their selections, depending on what feature are most important to them. Although we made an effort to interview parents of children with a variety of acute and chronic health issues, the inpatient population at our hospital, a tertiary care center in the Northeast United States, contains a high percentage of children with severe genetic or congenital diseases. However, we do feel that their insight provided important information about the cognitive processes underlying preference setting. Furthermore, we expect that people who participate in genomic research in the future will likely self-select to participate in research, as our subjects did, and therefore may hold similar views. We are also aware of the psychological effect of avoiding cognitive dissonance, in which some of our participants may have reported satisfaction when presented with a result or outcome that was directly indicated by their preferences, even if they might not have been wholly satisfied. This could prove troublesome as we move out of hypothetical result return and begin to disseminate actual research results to participants, so further studies should incorporate more sophisticated satisfaction measures.

Best Practices

We have developed a model for preference setting in genomic research that resonates with participants and is relatively intuitive. Although our study is preliminary and further testing is needed to determine if the model holds up in a larger cohort of participants and when actual results are returned, our study suggests that incorporating preference setting into the return of genomic results may be scalable and may be able to be implemented in a large-scale genomic biobank. We recommend that, if feasible, researchers implement methods that allow participants some choice in types of results to receive from genomic research which may increase participant benefits from participating in genomic research.

Research Agenda

This preliminary research study is a first step in addressing an increasingly important issue: Understanding how participants conceptualize their preferences for return of research results, which will be key to maximize benefit and minimize harm in large-scale genomic research where results are returned to participants. Future steps should include further assessing preference-setting models, how preference-setting models can be implemented in genomics research with the return of results, and how feasible it is to implement preference models in a large-scale genomic biobank. In addition, future steps should also assess participants' ability to navigate the preference-setting model in a context where in-person clarification is not immediately available. The benefits and harms of return of research results using these models should be assessed. The finding that participants had a limited understanding of risk and scientific validity, and that these concepts were not important to them, should be further studied, including potentially developing ways to increase understanding of the importance of risk and validity among participants. Finally, future approaches to studying participant decision making should include participants who are less well-educated, less familiar with genetics, and less comfortable with computers, thus better representing the U.S. population.

Educational Implications

For biobanks to return IRRs on the basis of participant preferences, a system must be created that can overcome the labor burden of case-by-case evaluation. This type of model removes that burden from researchers by providing them with clear and categorical instructions regarding which results to disclose. This model also teaches participants to consider the potential beneficial and harmful implications of IRRs.

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Sonja I. Ziniel is an instructor in pediatrics at the Harvard Medical School, a senior survey methodologist in the Center for Patient Safety and Quality Research at BCH, and a faculty member of the Division of Adolescent and Young Adult Medicine at BCH. She provided methodological expertise for this project with regard to the study design and data analysis, edited this article, and approved the final version.

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Elissa R. Weitzman is PI of multiple investigations centered on pioneering "citizen science" approaches for population health research including through use of novel patient-facing health information technologies and social media that involve return of research results to subjects. She is PI of an NIAAA funded investigation of mental health and substance use risk among youth with chronic medical conditions, and an NLM funded investigation testing an approach to engaging participants in a pediatric chronic disease registry in reporting patient-centered outcomes to drive comparative effectiveness research. Her role in this project included assistance with conceptualizing the research model and measurement framework, review of data to refine the model for specifying preferences for return of research results to biobank participants, interpretation of findings and review/approval of the final manuscript.

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