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Generating a Taxonomy for Genetic Conditions Relevant to Reproductive Planning

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Abstract

As genome or exome sequencing (hereafter genome-scale sequencing) becomes more integrated into standard care, carrier testing is an important possible application. Carrier testing using genome-scale sequencing can identify a large number of conditions, but choosing which conditions/genes to evaluate as well as which results to disclose can be complicated. Carrier testing generally occurs in the context of reproductive decision-making and involves patient values in a way that other types of genetic testing may not. The Kaiser Permanente Clinical Sequencing Exploratory Research program is conducting a randomized clinical trial of preconception carrier testing that allows participants to select their preferences for results from among broad descriptive categories rather than selecting individual conditions. This paper describes 1) the criteria developed by the research team, the return of results committee (RORC), and stakeholders for defining the categories; 2) the process of refining the categories based on input from patient focus groups and validation through a patient survey; and, 3) how the RORC then assigned specific gene-condition pairs to taxonomy categories being piloted in the trial. The development of four

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categories (serious, moderate/mild, unpredictable, late onset) for sharing results allows patients to select results based on their values without separately deciding their interest in knowing their carrier status for hundreds of conditions. A fifth category, lifespan limiting, was always shared. The lessons learned may be applicable in other results disclosure situations, such as incidental findings.

INTRODUCTION

Genome-scale sequencing is currently offered primarily in research contexts and its clinical use is focused on molecular diagnosis for unresolved clinical questions. This approach can also be used for carrier testing for autosomal recessive or X-linked conditions [Green et al. 2013], but there is limited experience in this context. Although carrier testing for specific diseases, such as cystic fibrosis (CF) and β-thalassemia [Mennuti 2008], is well-established in practice, there are scant data about what carrier testing results patients would find valuable if given the choice of genome-scale sequencing, which can assess hundreds of autosomal recessive or X-linked conditions. Data are also lacking on how to disclose the results of genome-scale sequencing in ways that are meaningful to clinicians and respectful of patient preferences.

Population-specific carrier panel testing has a well-established history, and these panels test for conditions whose outcomes range widely, from expected death in childhood to those with milder manifestations. For example, test panels developed for the Ashkenazi population typically included Tay-Sachs disease, CF, Gaucher disease and others [Klugman and Gross 2010]. Tay-Sachs disease is usually fatal by 6 years of age [2009]; CF causes chronic respiratory and digestive problems, but people with CF have an increasingly improved life expectancy because of evolving medical interventions [2011]. Gaucher disease has such phenotypic variability that it may result in childhood death (a rare subtype) or normal lifespan with no recognition of the condition [2009]. Initially, panels comprising 3–12 tests were offered as "all or nothing," and laboratories often charged more to test for less than the full panel [Leib et al. 2005]. This restricted patient choice for obtaining only the results of interest to them, as customization was, in effect, a billable service.

Some commercial laboratories now offer carrier panels comprising more than 100 conditions. The challenge with this approach remains the same: certain patients may be interested in testing for some, but not all, conditions. Furthermore, it is difficult to provide informed consent for every condition without an extended counseling visit [Elias and Annas 1994].

As part of a randomized clinical trial to offer genome-scale sequencing for preconception carrier testing, our research team created a taxonomy of genetic conditions using categories to guide decisions rather than asking people to decide disease-by-disease. The intent was to learn how to leverage genome-scale sequencing effectively while supporting individual

preferences. Sorting conditions into broader categories can potentially reduce the burden on patients and providers by allowing patients to select preferences from among these categories in keeping with patient autonomy in a reproductive, values-based context.

This paper describes the evolution of the taxonomy of condition categories, which included incremental iterations based on conceptual analyses by an interdisciplinary team concerning what characteristics are likely to matter most to patients for reproductive decision-making, augmented by empirical data from patients. Delineating the complex process of developing this taxonomy of condition categories is important so that others might consider the complexities involved in sharing category-based results—many of which touch upon patient values—in other contexts.. Creating this taxonomy began with an awareness of the ethical complexity of reproductive decision making. In addition to the personal values that may guide decisions, there are also political sensitivities surrounding the issues of abortion as well as the use of public funding for special education options to support children with health conditions or disabilities [Pergament 2013].

Stakeholders, including patients, clinicians, policymakers, and advocacy groups representing populations with diseases or disabilities have an interest in which conditions are included in testing choices and how those conditions are described. Three issues raise ethical concerns in the context of reproductive genetic testing. First are questions about which diseases to include or exclude from testing, such as adult onset diseases and diseases with unpredictable impact. The second is how to describe those diseases that are included, such as what constitutes a "severe" disease. Third are concerns about which variants to disclose: commitments to open disclosure must be balanced with constraining information to interpretable findings to limit the impact of uncertain findings on reproductive decision making. In addition, all three of these areas of concern include issues surrounding the potential impact on those tested and on populations with genetically linked diseases or disabilities.

Conditions with unpredictable impact or impact in adulthood have not been traditionally included in most carrier testing programs. In considering adult onset conditions, respecting the child's "right to an open future," particularly as children can be tested as adults when they choose for themselves, must be weighed against the potential benefit to children because parents can prepare children for disease or disability later in life [de Jong et al. 2011]. For conditions that are much more unpredictable (i.e., Gaucher disease), parents will need to balance the value of knowing about such a condition in their child with the potential for unnecessary anxiety and stigmatization.

Determining what conditions are described as "serious" is complicated by the subjectivity of the label and the potentially wide-ranging societal implications of that label. Those who advocate for the rights of disabled populations are concerned that the inclusion on carrier panels of disabilities that are associated with limited medical implications (e.g., nonsyndromic deafness, achondroplasia), sends messages to disabled populations and to parents that they are of lesser societal value with a disproportionate focus on the disability rather than on the person [Boardman 2014; McGuinness 2013]. Because this devaluing occurs in the context of societies that already have histories of discriminating against those

with disabilities [Munger et al. 2007; Parens and Asch 2003], undermining the value of these populations could be an unintended and negative consequence of genetic testing to inform reproductive planning.

When considering what variants to include, some would argue that more information can only promote parental choice, and this has been framed as "knowledge is power" by its advocates. But others point to the challenge of including variants of unknown significance and misinterpretations that may increase anxiety or lead to decisions to terminate pregnancies that are later regretted as more information and potential interventions become available. In light of these complexities and in support of informed patient decision making, determining the most appropriate categories to share in the context of reproductive planning is crucial. Broad categories that focus on the characteristics of most concern to potential parents can allow genetic counselors to fulfill what has been described as a "dual role"— serving as disability advocates while also supporting reproductive choice based on parental needs [Peterson 2012].

Our team grappled with these issues in developing a clinical trial that attempted to promote decision making that would be consistent with patient values and mindful of the challenges of population carrier testing [Press et al. 2011].

METHODS

The development of the taxonomy had two main phases (see Figure 1). During the first phase (Tables I–IV), the initial taxonomy from the project proposal was revised to reflect important distinctions between categories based upon potential clinical relevance and patient preferences. Revisions during this phase relied on a consensus process involving the entire study team, including a panel of experts called the Return of Results Committee (RORC). The RORC comprises a panel of experts in clinical and laboratory genetics, pediatrics, and obstetrics whose charge is to provide clinical and scientific guidance about result interpretations, guide decisions about whether to share results, and if results are to be shared, advise on what category results should be placed in. The second phase of the taxonomy development involved refinement and validation using patient input (Table V) and assignment of conditions to categories by the RORC (Table VI).

RESULTS

PHASE ONE – INITIAL TAXONOMY REVISIONS

Initial taxonomy—The research team started with a four-part taxonomy (see Table I) that drew upon the team's expertise and that was also informed by the genetic testing literature. Decisions made at this early stage included choosing the category name for conditions that lead to early death; although "childhood lethal" was considered first, the research team eventually chose "lifespan limiting" as a more emotionally neutral description. Three categories focused on the severity of the conditions as the main delimiting factor, and an additional fourth category ("quality of life") served as a catch-all for those conditions that were not considered medically severe but did impact life experience significantly. The proposed strategy was that study participants would always be given results for the most

serious category, lifespan limiting, but could choose what to receive from the remaining three categories. The main challenge at this preliminary stage was creating categories that grouped conditions in a way that was both clinically accurate and meaningful to patients.

Distinguishing between impairments and medically involved conditions—Once the project started, the research team, comprising pediatricians, genetic counselors, medical geneticists, health services researchers, a bioethicist, a psychologist, and an anthropologist, created a second version of the taxonomy to provide more clarity in the descriptions for each category (see Table II). The category "treatable" was now labeled as "medically involved" to convey that the child would have recurrent interaction with the health care system and require regular attention to medical issues, with treatments that might range from special diets to occasional hospitalizations. "Quality of life" was reframed as "impairment," to acknowledge that all conditions, not only less severe ones, can affect quality of life and that some conditions resulted in impairments without necessarily impacting quality of life adversely. In addition, some elements in the category "late onset or variable expression" were moved to a new standalone category, "variable impacts," to recognize that variability in disease expression and outcomes represented a distinction worth considering apart from the other categories. Appreciating some variability for the first three condition categories, the research team further illustrated those categories by including descriptions of the experience of most children.

Distinguishing between cognitive and physical impairments and including variability for all categories—After further discussion, the research team determined that two categories needed additional clarification. The research team decided that for impairments, physical and cognitive should be distinguished from each other, while for variability, age of onset and variability of impact should also be distinguished (see Table III). The categories were all now deliberately ranked in descending order of severity, and in this new schema, intellectual impairments were defined as those that precluded independent adult functioning. Based on this definition of intellectual impairment, "medically involved" was considered "less severe" because, although medically involved included conditions that would require regular medical interactions, intellectual impairments were seen as creating lifelong dependency. The key difference that the research group focused on was whether a child would need parental or external care for his entire life or would be able to transition to an independent adulthood.

At this point in the taxonomy creation, variability became a modifier in terms of impact and age for each condition rather than its own category. However, by distinguishing variability for each condition category, the taxonomy now included 12 categories. The research team became concerned that this level of granularity would create more confusion than clarity, not least because many condition phenotypes involve more than one category, making it difficult to know where to place those conditions.

Distinguishing severity of impacts—The RORC reviewed the new categories and advised further refinements. Rather than emphasize variability, the committee advised that each category should instead focus on distinguishing between severe and mild (see Table IV). The committee further recommended that the "shortened lifespan" category should have

three distinctions: children who do not live past 5 years of age, children who do not live to 18 years, and adults who do not live past 40. Although some distinctions were removed (variability of impact and age of onset for each condition category), the life expectancy and mild or severe specifications added further complexities. In addition, variable impact was no longer a focus for each category, as the RORC pointed out that genetic counselors routinely manage discussions of variability as part of the counseling process. Instead, variable age of onset transitioned into a separate category: "adult onset conditions."

PHASE TWO – TAXONOMY REFINEMENT, VALIDATION, AND TESTING

Refinement reflecting patient input and emphasizing severity and unpredictability—The research team held three focus groups with 15 women and one man (n=16) who had recently received carrier testing as part of their usual medical care to review the taxonomy categories [Schneider et al.]. All participants were members of Kaiser Permanente Northwest residing in Oregon or Southwest Washington and were asked for their opinions about the second and third versions of the taxonomy (Tables II and III). The focus groups confirmed that severity and age of onset were key distinguishing factors and that "shortened lifespan" was important as a discrete category. Variability was regarded as less critical, and participants indicated that the research team should consider the most severe version of the condition that is routinely seen to determine the criteria for categorization. They reinforced the view of the RORC that variability could be addressed in genetic counseling. The focus groups also suggested having results expressed in a straightforward manner, in hopeful terms that were readily understandable but not deceptively optimistic. They wanted to better understand potential impacts on family life, a consideration that was not originally prioritized in the taxonomy.

The taxonomy was revised based on this input and the advice of the RORC (see Table V). The resulting taxonomy emphasized "serious conditions" as a separate category. This was considered a broad default category. Most conditions would fall within this new category unless they were associated with early death ("conditions with significantly shortened lifespans") or very mild. "Conditions with unpredictable outcomes" included conditions that could manifest in a broad spectrum from mild (or unaffected) to severe, *and* where it would not be possible to predict outcome based on genotype. The research team retained late onset as a category because focus group participants were divided about whether they would want to learn about these conditions in preconception testing, indicating that it could be useful in facilitating decisions about testing.

At this stage, the research team also added examples to each category to highlight key characteristics and demonstrate how the categories would be applied. In both categories and their examples, the distinction between intellectual and physical impairments was abandoned because the focus had shifted to severity of condition. The research team modified the definitions and explanations in the taxonomy to emphasize that all of the genetic conditions would have an impact on both child and family life, but that with family, medical, and social support, even children with serious conditions would have meaningful and valuable lives. This is the version of the taxonomy that the research team is currently using with participants in the ongoing clinical trial.

Validation using a survey about perceptions of genetic conditions—
Concomitant with the focus groups, the research team deployed a survey to validate the taxonomy categories among a broader participant base compared with the limited number of subjects in the focus groups. Through a process of expert consensus, the research team identified 20 genetic conditions that exemplified characteristics likely to drive prospective parents' decisions about carrier testing. Five versions of the survey that each included 4 of the 20 conditions were administered to 193 people who had received carrier testing in the past. They reviewed the condition descriptions and rated them on a variety of attributes, such as how respondents would perceive the condition (severe, variable, controllable, visible, etc.). Survey participants independently perceived attributes that were consistent with the key characteristics of each category developed by the research team. More detailed results of this survey are reported in this same issue of this journal [Leo et al.].

Assignment of conditions to each category—The RORC developed a list of gene/ condition pairs from sources including existing commercial panels, published literature, and clinical experience. The process of choosing where to place each gene/condition pair in the taxonomy categories was complicated. Considerations included determining how much and what data was needed to be able to place a gene/condition pair into a particular category; how to handle conditions associated with multiple genes; how to handle variants in the same gene that may cause more or less severe phenotypes; and how to handle gene-condition pairs that could fit into multiple categories. The RORC considered these issues and advised that categories needed more specific definitions for the purpose of assignments. Furthermore, the RORC determined that a single category needed to be chosen in cases where category boundaries were crossed (e.g., allelic heterogeneity, genes with multiple phenotypic outcomes). Because many conditions fit into multiple categories, "serious" became the default assignment. This included X-linked conditions, which would assume the most severe outcome (male category).

However, gene-condition pairs that fit in multiple categories were flagged for variant review by the RORC. If a known milder variant was found during testing, and the participant did not select the mild category, results concerning that variant would not be disclosed. If a condition appeared lifespan limiting, but there were fewer than 3 cases, it was placed into the default serious category; lifespan limiting was defined as at least 50% of affected fetuses or children dying before the age of 10 years. The research team only required that the gene-condition pair be found in one person per family in order to categorize it.

The RORC used the condition thresholds described in the taxonomy in order to assign gene-condition pairs (see Table VI). For these assignments, each condition is placed in only one category. The exception is when there are several different forms of the same condition that can be distinguished from each other based on genotype (i.e., different genes or different mutations in the same gene). In this case, each distinguishable form of the condition can be placed in a separate category. For instance, the severe, infantile form of Gaucher disease would be in the 'lifespan limiting' category, whereas the mild, adult onset form of Gaucher would be in the 'late onset' category. Although specific percentages are listed in Table VI, these are meant as clarifiers to the descriptive words rather than thresholds. In many instances, the chances of certain events happening will not be precisely reported. Thus,

descriptions like rarely, mostly, often, etc., will need to be interpreted based on the clarifications defined in Table VI. The process of assigning conditions to these categories is ongoing, and the results will be reported in a subsequent paper.

DISCUSSION

Use of categories to specify results disclosure represents an intentional approach to genome-scale sequencing that supports individual decisions without asking patients to accomplish the impractical task of deliberatively deciding about each condition individually. This approach seeks to use genome-scale sequencing with nuance rather than using the technology to disclose everything simply because it can be done. One benefit of choosing from categories of conditions rather than specific conditions is that generic categorical information (e.g., severity of impact, age at onset) can be more meaningfully described and considered, because the broad categories can be based on features of the conditions with which most people can identify. Specific diseases may have technical and confusing names and features, while the categories can be described in non-specialist, accessible language. As the number of conditions for which testing can be performed increases, the challenge involved in asking patients to make decisions about individual conditions becomes impractical, and the ability to ensure adequate understanding for consent becomes more challenging.

Our proposed approach has an element of arbitrariness that the research team explicitly acknowledges. Although the taxonomy categories were devised and refined based on extensive feedback, the lines drawn between categories are still subjective boundaries. As the process of taxonomy creation illustrates, categories shifted from one iteration to the next, sometimes adding new distinctions and sometimes returning to prior ones. The detailed descriptions and examples of conditions for each category can help others operationalize the taxonomy. Our research team expects that use of the taxonomy in our trial and formally evaluating its utility will help refine categorizations further in an ongoing, iterative process.

Determining which conditions are significant enough that patients should be offered testing to inform reproductive planning can be challenging and is ethically charged. We addressed this by having a diverse "serious" category (that includes cystic fibrosis and phenylkentonuria) as a way to accommodate this tension. The primary determinant became not a question of disease "severity," but rather whether or not a condition would have a significant impact on a person's life, particularly in terms of the need for medical treatment and management. In this way, the truly severe conditions (life span limiting) were constrained to conditions that caused death in childhood. Our approach to the ethical issues related to the inclusion of adult onset, unpredictable and mild conditions was to highlight these categories for patients, so they can decide if the distinctions are meaningful to them. As genome-scale sequencing moves closer to becoming a part of usual care [Manolio et al. 2013], it is increasingly important to consider how to accommodate patient preferences for carrier testing and support informed decision-making.

Stakeholder input was critical in creating the optimal taxonomy categories and content. Patients' suggestions about the taxonomy highlight the fact that test results affect people's

lives, and test results about genetic conditions may provide valuable information that can shape both reproductive and life decisions with long-term and wide-ranging consequences [Press et al. 2011]. Therefore, great care should be taken to identify and accommodate patient information needs through careful presentation of the choices among results available to patients. The RORC, which used the categories for results assignment, required a greater level of specificity than that used to explain the categories to patients.

One limitation in the process of taxonomy creation and refinement that should be noted concerns timing. Because the timeline for our project deliverables was compressed, the survey and focus groups happened at the same time, rather than sequentially. The survey was implemented using an earlier version of the taxonomy, which was subsequently refined with input from the focus groups. It would have been optimal to refine the taxonomy with the focus groups first and then use the survey to confirm the focus group findings. This would have provided broader validation of the taxonomy categories as well as identified areas needing further refinement. Doing things in this order would have ensured that the focus groups would not identify elements that could have radically altered the taxonomy and, hence, the survey content used to provide a more direct validation of the RORC final taxonomy.

Conclusions and future directions

The iterative approaches to the development of the taxonomy allowed the research team to consider different ways of arranging information to add value and meaning to the categories described. Categories were then refined and confirmed through qualitative focus groups and a survey whose findings provided empirical support that validated the categories. In the current taxonomy, which is now being tested, issues related to the severity and unpredictability of conditions were prioritized. This process shows how categories expanded and contracted as the research team struggled to create categories that were meaningful from clinician, laboratory, and patient viewpoints. Future research might explore whether giving people control of the results returned is helpful and, if so, whether the categories themselves contribute to usefulness in the context of preconception carrier testing. In addition, other clinical studies could investigate the process of taxonomy creation to determine if the main features of the categories derived are useful to other teams using genome-scale sequencing in different clinical contexts. Finally, other studies are needed to test alternative approaches and evaluate our taxonomy in other patient populations with higher ethnic and racial diversity than the Pacific Northwest.

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REFERENCES

ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstetrics and gynecology. 2009; 114(4):950–953. [PubMed: 19888064]

ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. Obstetrics and gynecology. 2011; 117(4):1028–1031. [PubMed: 21422883]

Boardman FK. The expressivist objection to prenatal testing: the experiences of families living with genetic disease. Social science & medicine (1982). 2014; 107:18–25. [PubMed: 24602967]

de Jong A, Dondorp WJ, Frints SG, de Die-Smulders CE, de Wert GM. Advances in prenatal screening: the ethical dimension. Nature reviews Genetics. 2011; 12(9):657–663.

Elias S, Annas GJ. Generic consent for genetic screening. The New England journal of medicine. 1994; 330(22):1611–1613. [PubMed: 8177253]

Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in medicine : official journal of the American College of Medical Genetics. 2013; 15(7):565–574. [PubMed: 23788249]

Klugman S, Gross SJ. Ashkenazi Jewish screening in the twenty-first century. Obstetrics and gynecology clinics of North America. 2010; 37(1):37–46. [PubMed: 20494256]

Leib JR, Gollust SE, Hull SC, Wilfond BS. Carrier screening panels for Ashkenazi Jews: is more better? Genetics in medicine : official journal of the American College of Medical Genetics. 2005; 7(3):185–190. [PubMed: 15775754]

Leo M, McMullen C, Wilfond B, Lynch F, Reiss J, Gilmore M, Himes P, Kauffman T, Davis J, Jarvik G, Berg J, Harding C, Kennedy K, Kostiner D, Quigley D, Richards C, Rope A, Goddard K. Patient Ratings of Autosomal Recessive or X-linked Conditions: Empirical Validation of a Genetic Conditions Taxonomy. American Journal of Medical Genetics. Under submission.

Manolio TA, Chisholm RL, Ozenberger B, Roden DM, Williams MS, Wilson R, Bick D, Bottinger EP, Brilliant MH, Eng C, Frazer KA, Korf B, Ledbetter DH, Lupski JR, Marsh C, Mrazek D, Murray MF, O'Donnell PH, Rader DJ, Relling MV, Shuldiner AR, Valle D, Weinshilboum R, Green ED, Ginsburg GS. Implementing genomic medicine in the clinic: the future is here. Genetics in medicine : official journal of the American College of Medical Genetics. 2013; 15(4):258–267. [PubMed: 23306799]

McGuinness S. Law, reproduction, and disability: fatally 'handicapped'? Medical law review. 2013; 21(2):213–242. [PubMed: 23288299]

Mennuti MT. Genetic screening in reproductive health care. Clinical obstetrics and gynecology. 2008; 51(1):3–23. [PubMed: 18303496]

Munger KM, Gill CJ, Ormond KE, Kirschner KL. The next exclusion debate: assessing technology, ethics, and intellectual disability after the Human Genome Project. Mental retardation and developmental disabilities research reviews. 2007; 13(2):121–128. [PubMed: 17563891]

Parens E, Asch A. Disability rights critique of prenatal genetic testing: reflections and recommendations. Mental retardation and developmental disabilities research reviews. 2003; 9(1):40–47. [PubMed: 12587137]

Pergament D. What does choice really mean? Prenatal testing, disability, and special education without illusions. Health matrix (Cleveland, Ohio : 1991). 2013; 23(1):55–117.

Peterson M. Disability advocacy and reproductive choice: engaging with the expressivist objection. J Genet Couns. 2012; 21(1):13–16. [PubMed: 22037896]

Press, N.; Wilfond, B.; Murray, M.; Burke, W. The power of knowledge: how carrier and prenatal screening altered the clinical goals of genetic testing. In: Burke, W.; Edwards, K.; Goering, S.; Holland, S.; Trinidad, S., editors. Achieving justice in genomic translation: rethinking the pathway to benefit. New York, NY: Oxford University Press; 2011. p. 95-107.

Schneider J, Goddard K, Davis J, Wilfond B, Kauffman T, Reiss J, Gilmore M, Himes P, Lynch F, Leo M, McMullen C. "Is it worth knowing?" Focus group participants' perceived utility of genomic preconception carrier screening. Journal of Genetic Counseling. Under submission.
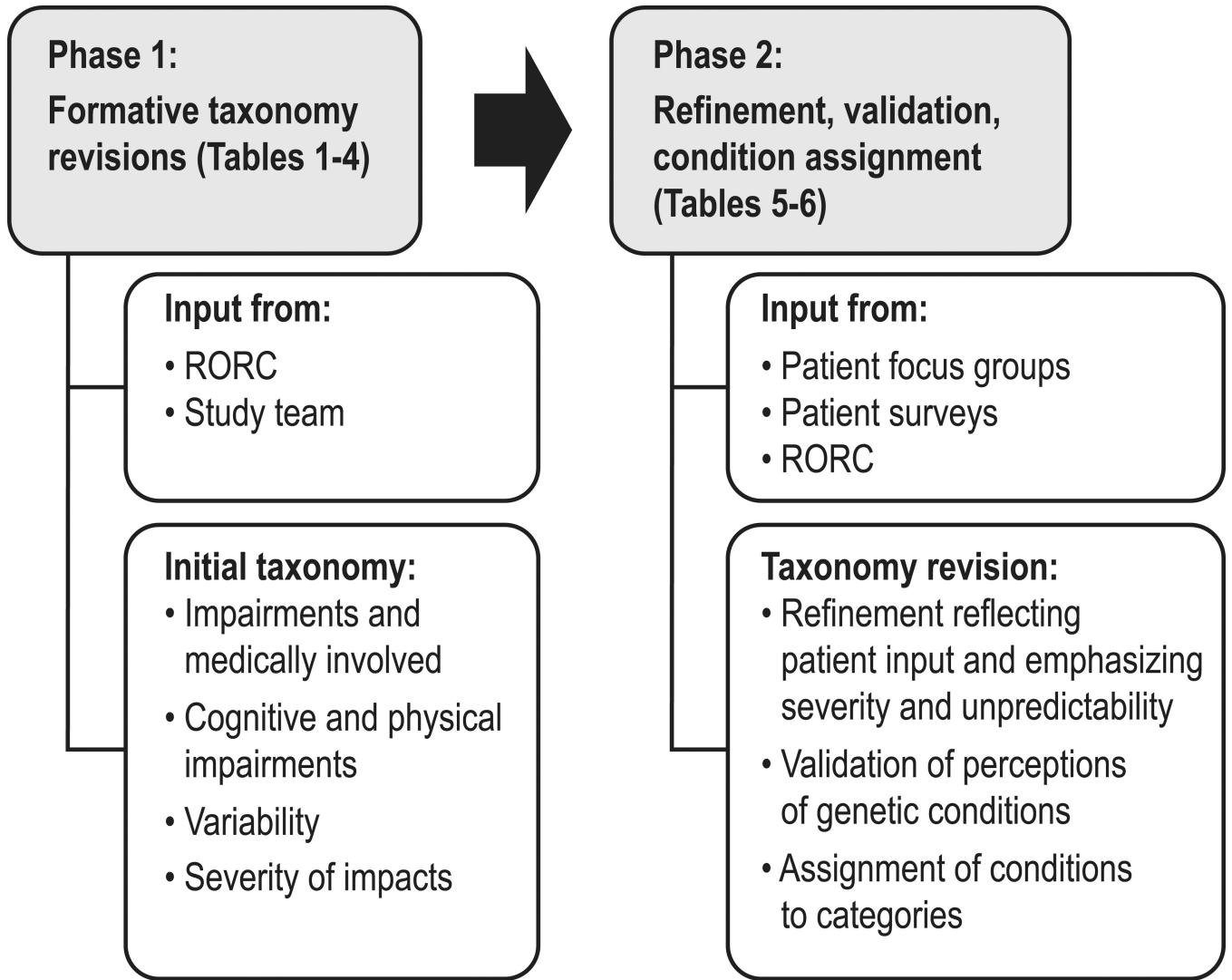
Phase 1:
Formative taxonomy revisions (Tables 1-4)

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Phase 2:
Refinement, validation, condition assignment (Tables 5-6)

Input from:
• RORC
• Study team

Input from:
• Patient focus groups
• Patient surveys
• RORC

Initial taxonomy:
• Impairments and medically involved
• Cognitive and physical impairments
• Variability
• Severity of impacts

Taxonomy revision:
• Refinement reflecting patient input and emphasizing severity and unpredictability
• Validation of perceptions of genetic conditions
• Assignment of conditions to categories

Figure 1.
The process of taxonomy development

Table I

Initial proposed taxonomy

Categories of genetic conditions
Lifespan limiting Severe conditions that lead to death in childhood. Also includes conditions where the fetal genotype might adversely impact the pregnancy.
Treatable Conditions that are severe if untreated but have a known treatment, usually diet. Many are part of newborn screening.
Late onset or variable expression Conditions that do not greatly limit lifespan, or conditions that might be severe, at least for some people, but might also be near-normal in phenotype.
Quality of life Conditions that do not significantly limit lifespan, but do impact quality of life, such as hearing loss, vision loss, developmental delay, loss of gross motor control, etc.

Table II

Distinguishing between impairments and medically involved conditions

Categories of genetic conditions
Shortened lifespan Most children have a shortened lifespan and few live into adulthood, even with medical interventions.
Medically involved Most children take daily medications or use special diets and require regular medical care, and some may need occasional hospitalizations. Some of these conditions are detected by newborn screening.
Impairments Most children will have impairments that will affect their lives, such as reduced hearing, vision, mobility, or intellectual functioning.
Variable impacts Some children may have shortened lifespans, be medically involved, or have impairments, but others will have no problems during childhood.

Table III

Distinguishing between cognitive and physical impairments and including variability for all categories

Categories of genetic conditions	Variable impact (fewer than half of children will be affected)	Variable age (fewer than half so affected as children)
Shortened lifespan Most children have a shortened lifespan and few live into adulthood, even with medical interventions.		
Intellectual impairments Most children will have intellectual impairments that will result in long-term dependency on others for care.		
Medically involved Most children take daily medications or use special diets, and require regular medical care, and some may need occasional hospitalizations. Some of these conditions are detected by newborn screening.		
Physical impairments Most children will have impairments that will affect their lives significantly, such as hearing, vision, or mobility impairments.		

Table IV

Distinguishing severity of impacts

Categories of genetic conditions		
Shortened lifespan Many children do not live past 5 years of age, even with medical interventions Many children do not live past 18 years of age, even with medical interventions Many adults do not live past 40 years of age, even with medical interventions		
	Serious	**Mild**
Intellectual impairments	Many children will have long-term dependency on others for care	Many children will not be high achievers in school but can function independently as adults
Medically involved	Many children take daily medications or use special diets, and typically see a doctor four or more times a year and may need occasional hospitalizations	Many children will need to follow a special diet or take daily medications, and typically need to see a doctor fewer than four times a year
Physical impairments	Many children will have impairments that will affect their lives daily, such as serious hearing, vision, or mobility problems	Many children will be clumsy and not excel in sports or have reduced vision or hearing
Adult onset conditions	Most people do not develop symptoms until adulthood, but these symptoms typically include serious intellectual or physical impairments, or are very medically involved	Most people do not develop symptoms until adulthood, and these symptoms typically include mild intellectual or physical impairment or are mildly medically involved

Table V

Taxonomy used with participants (reflecting patient input and emphasizing severity and unpredictability)

Categories of Genetic Conditions	Do you wish to receive these results?
<u>**Conditions with significantly shortened lifespan**</u> **Most children do not live past early childhood, even with medical interventions** <u>Tay-Sachs</u> results in the gradual loss of movement and mental function. Infants develop increasing seizures, vision and hearing loss, and severe mental disability. Death usually occurs by age 4.	Everyone will receive
<u>**Serious conditions**</u> **Most children will have medical problems that require regular medical visits, daily medications, carefully monitored diets, or surgeries; or will have serious problems with learning, vision, hearing or mobility. Children may have shortened life spans into early adulthood.** <u>Duchenne Muscular Dystrophy</u> causes gradual loss of muscle function, beginning at five years of age. Children benefit from wheel chairs, and medications can support breathing and cardiac function, but most people do not live past their 20s. People with <u>Phenylketonuria (PKU)</u> follow a very restrictive low protein diet for life to avoid problems with learning and behavior. <u>Usher Syndrome</u> causes severe hearing loss from birth and vision loss later in childhood. In adolescence, people develop night blindness and a gradual loss of peripheral (side) vision. <u>Batten Disease</u> causes gradual loss of brain functions, beginning between 5–10 years of age with gradually worsening seizures, visual problems, and learning. Most children do not live past their teens or 20s. <u>Cystic Fibrosis</u> affects the lungs and digestive system. People with CF require frequent doctor visits and typically take many medications. The average life expectancy is 35 years, but this continues to improve with new treatments.	☐ Yes ☐ No
<u>**Mild conditions**</u> **Most children will have medical problems that require occasional extra medical visits, occasional medications, a slightly modified diet, or surgery; or will have mild problems with learning, vision, hearing, or mobility.** People with <u>Ataxia with Vitamin E Deficiency</u> develop clumsy hand movement, and reduced awareness of body positioning as older children. Later symptoms may include difficulty speaking and loss of some vision. These problems can be reduced with taking Vitamin E daily. <u>Ichthyosis</u> is characterized by scaling of the skin, particularly on the neck, trunk and lower extremities. Typically this scaling improves with age and during the summer months. This condition typically does not affect intelligence or behavior.	☐ Yes ☐ No
<u>**Conditions with unpredictable outcomes**</u> **It is difficult to predict the outcome for many children. Some children will have more serious versions but others will have more mild versions or no problems at all.** <u>Gaucher Disease Type 1</u> causes degenerative bone disease and low blood counts. While some people develop symptoms in childhood others have few symptoms even as adults. For those who do have these symptoms, treatments can reduce symptoms. <u>Limb Girdle Muscular Dystrophy</u> cause muscle weakness that affects the ability to walk and run. Some people are affected as children but others are not affected until adulthood. Some people lose the ability to walk within 10 years, but other people have less serious problems.	☐ Yes ☐ No
<u>**Conditions that begin as adults**</u> **Few have any symptoms as children, but medical, behavioral, vision, or hearing problems may begin as adults.** <u>Hemochromatosis</u> causes liver, heart, and pancreas problems. The first symptoms typically begin between the ages of 30 and 50, and can be treated relatively effectively, if they even develop at all. <u>Alpha-1 Antitrypsin Deficiency</u> causes emphysema (progressive breathing difficulty and a frequent	☐ Yes ☐ No

Categories of Genetic Conditions	Do you wish to receive these results?
cough) with symptoms typically developing after age 60 in non-smokers and after age 40 in smokers.	

Table VI

Definitions used by RORC for category assignment

Categories of genetic conditions
Lifespan limiting (childhood) Greater than 50% die before age 10. Some people may live longer, but usually die before their 20s or 30s.
Serious This is the default category. Conditions will likely end up in this category unless the condition appears to have a better fit to one of the categories below. If there is variation in phenotype, the majority (>50%) have the most severe form.
Moderate/Mild Signs and symptoms of the condition are typically not life threatening, although in rare instances they might be life threatening. Patients with the condition typically experience only mild or moderate disruption to normal activities and functions (e.g., poor vision vs. blindness). If there is treatment available, the treatment itself is not considered highly burdensome in terms of the medical interventions or lifestyle modifications that are required. With treatment, patients may experience few or no symptoms of the condition.
Unpredictable There is a wide range in severity of phenotype. Factors that may vary include age at onset, severity of symptoms, or presence of symptoms. It is not possible to tell how severe the condition will be for a particular individual based on genotype. For instance, there may be families in which siblings carry the exact same mutations, but have vastly different expression of the phenotype. The majority (>50%) will not have the most severe form.
Late Onset Symptoms do not appear for most people (e.g., ~75–80%) until after age 20.