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Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/gim>

DISCLOSURE

The authors declare no conflict of interest.

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Abstract

As genomic and exomic testing expands in both the research and clinical arenas, determining whether, how, and which incidental findings to return to the ordering clinician and patient becomes increasingly important. Although opinion is varied on what should be returned to consenting patients or research participants, most experts agree that return of medically actionable results should be considered. There is insufficient evidence to fully inform evidence-based clinical practice guidelines regarding return of results from genome-scale sequencing, and thus generation of such evidence is imperative, given the rapidity with which genome-scale diagnostic tests are being incorporated into clinical care. We present an overview of the approaches to incidental findings by members of the Clinical Sequencing Exploratory Research network, funded by the National Human Genome Research Institute, to generate discussion of these approaches by the clinical genomics community. We also report specific lists of “medically actionable” genes that have been generated by a subset of investigators in order to explore what types of findings have been included or excluded in various contexts. A discussion of the general principles regarding reporting of novel variants, challenging cases (genes for which consensus was difficult to achieve across Clinical Sequencing Exploratory Research network sites), solicitation of preferences from participants regarding return of incidental findings, and the timing and context of return of incidental findings are provided.

Keywords

actionability; actionable genes; clinical sequencing; genomic medicine; incidental findings

BACKGROUND

Massively parallel DNA-sequencing technologies have been widely adopted in research and are increasingly being used in a clinical context.¹ However, the vast scale of the human genome poses considerable interpretative challenges and necessitates novel approaches to analysis, patient education, and genetic counseling. Among the most pressing concerns is the potential discovery of incidental findings (IFs) unrelated to the indication for obtaining the genomic test, previously termed the “incidentalome.”² The clinical significance of genomic IFs varies, as with incidental radiographic findings that may range from a mild deviation that is not commented upon by the radiologist, to a benign-appearing nodule that is commented on but requires no further evaluation, to a large unexpected mass that requires clinical

follow-up. Likewise, the types of genomic variants include a multitude of variants with little or no clinical implications as well as rare variants causally related to specific Mendelian disorders. Although testing of disease-specific gene panels may obviate the issue of IFs, these testing panels are evolving to encompass large numbers of genes and may be replaced by genome-scale tests—similar to the way that a broad chemistry panel is generally run, even when only a sodium level is ordered. As genome-scale testing is expanding in the clinical and research arenas, determining how and which IFs to return to the ordering clinician and patient becomes urgent.

In theory, all results could be shared with patients or subjects, but this approach is fraught with potential problems because of practical issues such as time constraints, lack of physician understanding, and the currently incomplete understanding of the consequences of most human variations. A central tension in the return of genomic IFs is between the ethical principles of “duty to warn” and “do no harm” on the part of physicians and the various choices of patients, some of whom wish to “know everything” in their genome and others who will undoubtedly wish to exercise their preference “not to know” certain findings. Complicating this landscape further is the difficulty of communicating to patients the vast array of possible results before embarking on testing so that they can make adequately informed decisions. Although opinion is varied on what should be returned to consenting subjects or patients, most geneticists agree that return of medically actionable results should be considered. However, a recent survey has found a significant degree of both consensus and difference in preferences among medical geneticists regarding specific examples of IFs.³

The Clinical Sequencing Exploratory Research (CSER) network includes a group of six U01 projects begun in 2011 and funded by the National Human Genome Research Institute and the National Cancer Institute, in which the impact of genome-scale testing is being examined in diverse clinical settings. These projects share a common goal of studying the implementation of genomic medicine; many address the topic of IFs in different clinical contexts and use distinct approaches to the analysis and reporting of these results. The impact of the return of IFs is being studied, with consideration of bioethical, economic, and patient-reported health and psychosocial outcomes. Examining and comparing the procedures used for determining which results to return—and in some cases, the actual gene lists arrived at by different members of the consortium—will be useful to the community because they represent implementation in a variety of contexts and may serve as examples of what “real-world” groups are doing as they tackle this complex issue.

To that end, we present an overview of the approaches to IFs from genome-scale sequencing by members of the CSER network. Our goal is to generate discussion of these approaches by the clinical genomics community and to explore the types of findings that might be included or excluded in various contexts. It should be noted that whether a given finding is considered “incidental” depends entirely on the clinical context, and that certain findings considered “incidental” in one clinical setting (e.g., a child with hearing loss) could have “diagnostic” significance in a different setting (e.g., an adult with colon cancer), and vice versa. Although most, if not all, CSER projects are actively exploring participant and/or provider preferences, we have not summarized those ongoing studies here.

We emphasize that the strategies and specific lists provided here should be seen only as starting points that must evolve and that will benefit from feedback. The American College of Medical Genetics and Genomics (ACMG) has recently published recommendations for clinical laboratories regarding the management of genomic IFs,⁴ and the Evaluation of Genomic Applications in Practice and Prevention Working Group has developed a streamlined evidence-based method for use in the development of guidelines.⁵ Both of these

statements acknowledge the limited knowledge base currently available to inform clinical practice. The CSER projects are, by design, carrying out research at the edge of clinical practice, and thus it is hoped that the results will lend insight into best practices for clinical genome sequencing. It is to be expected that there will be areas of disagreement among projects, and these challenging cases may help bring attention to salient features that define actionability. By providing examples of processes and context-dependent outputs, it is hoped that the CSER experience can benefit other groups that would like to implement similar procedures for the return of IFs. Although the primary focus of this exercise is not on patient/participant consent, the processes that are developed to guide return of results will directly influence the process of patient education and informed decision making.

PROJECTS AND PROCESSES

The CSER consortium represents a diverse collection of projects investigating the application of genome-scale sequencing in different clinical settings, including pediatric and adult sub-specialties, germline diagnostic testing, tumor sequencing, and specialty and primary care.

- The Baylor College of Medicine (BCM) Baylor Advancing Sequencing into Childhood Cancer Care project aims to incorporate Clinical Laboratory Improvement Amendments–certified tumor and blood exome sequencing into the care of children with newly diagnosed solid tumors.
- The Brigham and Women’s Hospital/Harvard Medical School (BWH/HMS) MedSeq Project is focused on the integration of whole-genome sequencing into the practice of medicine in two distinct domains: participants with a known genetic disease and generally healthy participants.
- The Children’s Hospital of Philadelphia (CHOP) PediSeq Project is investigating the use of genome-scale sequencing in the pediatric setting, with a focus on four heterogeneous pediatric disease cohorts (bilateral sensorineural hearing impairment, intellectual disability, nuclear-encoded mitochondrial respiratory chain disorders, and sudden cardiac arrest/death).
- The collaborative CanSeq project between the Dana-Farber Cancer Institute and the Broad Institute (DFCI/Broad) is specifically geared toward adult patients with advanced cancer, with the goal of improving cancer patient outcomes by identifying biologically consequential somatic (tumor) alterations that can be targeted by existing or emerging anti-cancer agents.
- The NCGENES (North Carolina clinical Genomic Evaluation by Next-generation Exome Sequencing) project at the University of North Carolina at Chapel Hill (UNC) investigates the use of exome sequencing in adults and children in four broad patient groups: hereditary cancer susceptibility, cardiogenetic disorders, neurogenetic disorders, and congenital malformations.
- The New EXome Technology in Medicine (NEXT Medicine) project at the University of Washington (UW) is a randomized controlled trial of exome sequencing in patients with colorectal cancer or polyposis for whom a genetic test is ordered in the course of usual clinical care.

Each project has established processes for determining the types of IFs to report (Table 1 and Supplementary Data and Supplementary Tables S1–S5, online). Committees with highly similar expertise are used for evaluating genes for return a priori (three projects) or on a case-by-case basis (three projects). Each project is using a unique framework for organizing

types of IFs and returning results that is specific to the goals and research questions being addressed (Table 2 and Supplementary Data and Supplementary Tables S1–S5, online).

CHALLENGING CASES

To further illuminate some of the similarities and differences in the processes used by the different study teams, we constructed a small number of “challenging cases” that depict examples for which actionability was considered particularly difficult to determine (Table 3). These examples demonstrate cases for which consensus may be difficult to achieve and highlight areas in which contextual factors (such as the age of the patient population) and the underlying framework may influence decisions about clinical actionability.

- Pharmacogenomic variants, such as those in cytochrome P450 2C19, were for the most part not deemed actionable because the chance that an individual will receive a given drug is low and, importantly, after prescription of that agent, there is typically a chance for a clinician to make a decision about whether pharmacogenomic testing should be obtained. Moreover, although pharmacogenomic testing may ultimately be incorporated routinely into patient care, there is no consensus at present on the utility of most such information. On the other hand, malignant hyperthermia due to *RYR1* mutations, which confers a high risk of morbidity with exposure to general anesthesia, was felt to be actionable by many groups due to the substantial chance of an individual undergoing general anesthesia; the incomplete penetrance of the condition, which could result in a negative family history of disease despite the mutation being present (thus escaping clinical detection); the lack of routine testing in current anesthesia practice; and the effectiveness of alternative anesthetic choices.
- Neurofibromatosis type 1 (NF1) is usually clinically recognizable, but many affected individuals escape clinical detection until the diagnosis is established in a family member. Due to discrete and specific recommendations for follow-up of individuals with NF1, some groups considered a pathogenic mutation in the NF1 gene to be an actionable IF, whereas other groups considered the recommended surveillance to have limited evidence of clinical utility in an asymptomatic individual.
- Familial Mediterranean fever often results in a long diagnostic odyssey with significant morbidity. This, coupled with the availability of an effective prophylactic treatment, led some groups to consider familial Mediterranean fever an actionable IF. Other groups felt that familial Mediterranean fever was sufficiently diagnosable by standard techniques upon presentation and thus the incidental discovery of a pathogenic mutation was not considered sufficiently actionable.
- The Factor V Leiden mutation results in an increased chance of deep venous thrombosis and possible serious morbidity due to embolism, and the absolute risk depends on whether the individual is heterozygous or homozygous. Current practice recommendations discourage screening for Factor V Leiden in otherwise-asymptomatic individuals.⁶ Researchers at all CSER sites felt that the increased chance of deep venous thrombosis was not sufficiently high in the heterozygous state to reach an actionable threshold, whereas researchers at most sites chose to include homozygous Factor V Leiden mutations as an actionable finding.
- Hemochromatosis has been well studied for possible population screening, but this has not been recommended due to low penetrance and the number of individuals needed to test in order to prevent morbidity.⁷ However, as discussed by the

Electronic Medical Records and Genomics (eMERGE) consortium,⁸ the threshold for return of a known result differs from that needed to justify population screening. Due primarily to the fact that hemochromatosis confers a modest risk of a very serious outcome that is highly preventable through minor intervention, members at all CSER sites considered a homozygous p.C282Y mutation in *HFE* to be actionable. However, compound heterozygosity for the p.C282Y with another mutation was considered less actionable due to the much lower penetrance.

- The presentation of Gaucher disease differs depending on the specific mutation, and the less severe forms can often be diagnosed in adulthood. Treatment with enzyme replacement therapy is expensive but can mitigate symptoms. Groups differed on whether homozygous pathogenic mutations would be considered actionable if detected in children versus adults. This difference may be due to a lack of published data to support the benefit of enzyme replacement therapy in adult patients with no prior diagnosis (despite anecdotal experiences with improvement in symptomatic patients diagnosed in adulthood).
- A number of cancer predisposition genes are actionable due to the impact of screening and prophylactic measures. However, certain susceptibility loci, such as *CHEK2*, were controversial due to the modest level of increased relative risk of cancer conferred by pathogenic variants and the lack of clinical guidelines regarding management of carriers of these mutations.
- Maturity-onset diabetes of the young is caused by mutations in a number of genes. Early detection could lead to prompt management and potential mitigation of morbidity and thus members at most CSER sites considered pathogenic mutations in *HNF1A* to be actionable. However, because maturity-onset diabetes of the young typically does not present with acute ketoacidosis, as is frequently the presenting symptom in type I diabetes, and routine medical care would be likely to identify affected individuals, the urgency of reporting this finding might be reduced.
- Finally, pathogenic mutations in genes associated with long QT syndrome convey a risk of sudden cardiac death that is potentially preventable, which suggests actionability. However, due to extensive locus heterogeneity, a number of genes have been associated with long QT syndrome only in rare cases; as a result, the existing knowledge base regarding the phenotypic spectrum of these subtypes of long QT syndrome (such as LQT13) is quite small, leading some groups to question whether to act on IFs in these genes.

DISCUSSION

In the context of IFs, it is clear that the vast majority of the variants detected by genome-scale sequencing will have no discernible clinical importance, and only a small number will have demonstrated health or reproductive implications. The approaches to returning IFs that are being explored by the CSER network should provide evidence and guidance on best practices for the clinical application of genome-scale sequencing tests. Several sites (CHOP, UNC, and UW) use a priori categorization of genes, using the concept of actionability in order to facilitate informed consent, analysis, and return of results. DFCI/Broad has adopted the list of genes recommended by the ACMG for return of IFs⁴ as a starting point for filtering germ-line noncancer IFs, with each alteration being evaluated on a case-by-case basis. BCM assesses IFs on a case-by-case basis within a general framework established by the BCM Medical Genetics Laboratory. BWH/HMS is returning all potentially clinically valid findings within predefined categories but does not use clinical actionability in making such decisions. None of the sites currently include patient groups or the public in their processes to determine medical actionability. In general, the determination of whether

specific gene mutations are actionable requires relevant medical and/or scientific expertise. Although most, if not all, CSER projects are actively exploring preferences of participants and/or referring providers about the type of results to disclose and the timing and method of such disclosure, we have not summarized those ongoing studies here.

Given the recent release of the recommendations by the ACMG for return of certain medically actionable IFs from genomic tests in clinical laboratories,⁴ we compared the approaches of the participating CSER groups regarding such findings. There are some similarities and some differences between the recommendations of the ACMG and the various choices of the CSER projects, particularly around the issues of providing participants the opportunity to “opt out” of receiving a small list of medically actionable IFs and how medically actionable adult-onset disorders should be returned to the clinicians of pediatric participants.

Variants of uncertain significance

The vast majority of genomic variants (such as novel or rare missense variants) will be of uncertain clinical significance. Because it is presumed that the participant has not been selected for a phenotype relevant to an IF, the prior probability that a given variant of uncertain significance (VUS) is actually a disease-causing one is extremely low. Moreover, in a clinical setting, it is critical not to overwhelm patients or their clinicians with false-positive or uninterpretable results, which are prone to misinterpretation. It has been documented that patients with VUSs in *BRCA1* or *BRCA2* have had surgical intervention, often despite low risk that the VUS was pathogenic,⁹ raising concerns regarding the hazards of incorrect interpretation of a VUS result by patients and/or clinicians. Even more benign interventions, such as increased radiological surveillance, are complicated by false positives, radiation exposure, and unnecessary follow-up studies, thus having the potential to cause anxiety for patients and add further health-care costs. Therefore, most of the groups in the CSER consortium have arrived at the conclusion that, in the case of IFs, only known disease-causing mutations or novel protein-truncating mutations with likely pathological effect should be returned. By contrast, the MedSeq Project seeks to capture participant and physician responses to “high-grade” VUSs related to Mendelian cardiac conditions in order to explore how physicians and participants cope with such uncertainty and the potential impact to the health-care system.

It is recognized that sensitivity is lost by setting a high bar for reporting of variants as IFs. However, maximizing specificity was felt by many groups to be critical in this endeavor. This contrasts with how VUSs are handled in a diagnostic setting, where maximizing sensitivity to a greater extent is desirable and VUSs in genes relevant to the presenting diagnosis would be reported. Thus, all of the CSER sites are returning VUS results for genes relevant to the clinical diagnosis of the participant being sequenced.

Context and timing of return of results

The CSER network groups are handling the context and timing of return of results differently in accord with the diverse study designs. Genetic counselors and physicians are both involved in the return of results to participants at BCM, CHOP, UNC, and UW. At BWH/HMS and DFCI/Broad, the ordering physicians return results to participants. In the case of BWH/HMS, this method of returning results is related to the study goals of understanding how genetically sophisticated and genetically naive physicians manage genomic information. The UNC, BCM, and DFCI/Broad studies return any actionable IFs at the same time as the diagnostic results, whereas UW returns IFs at a separate visit from the return of colorectal cancer or polyposis findings in order to allow the participant to better process the complex genetic information at each visit. CHOP offers participants the

opportunity to receive diagnostic results and IFs in a single visit or to have a follow-up visit. There is considerable diversity among CSER sites regarding the subsequent return of other non-medically actionable findings in a participant- and/ or physician-driven fashion. For example, the UW project prioritizes in-person delivery of results, whereas the NCGENES project is studying the return of non-medically actionable findings using categories and modes of delivery that are calibrated based on the chance that such results could cause psychosocial harm.

Right of refusal of medically actionable IFs

There exists a significant difference among the CSER sites regarding the ability of participants to refuse medically actionable IFs. Three sites (BCM, BWH/HMS, and UNC) do not offer the participant/family in the CSER protocol an opportunity to refuse medically actionable IFs once they have enrolled. CHOP and DFCI/Broad elicit preferences regarding categories of IFs that participants would like to receive but reserve the right to overrule a participant's refusal in the case of IFs that are ruled "immediately medically actionable." UW allows participants to refuse any type of IF and specifically offers participants the opportunity to decline different types of results by category at the return of the colorectal cancer or polyposis-related primary results and again just before return of the IFs. Ideally, in this situation, the participant will make a consistent decision and the medical geneticist returning the results will not receive the refused results from the laboratory; however, the participant may change his or her mind, which would place the provider in the tenuous position of not returning a result that has been provided by the laboratory.

Although members at some CSER sites believe that the return of these results is both necessary to their study design and an ethical obligation, conversations among group members do indicate substantial differences of opinion about the role of individual participant preferences for return of medically actionable IFs. Some investigators prioritize the participants' autonomy in deciding what to receive and express concern that participants may refuse a genomic test if they cannot refuse IFs. However, there are clearly ethical and legal differences in the responsibilities of researchers toward research participants versus those of clinicians toward patients. Because the CSER projects are exploring genome-scale sequencing in a clinical context, each CSER site must face such choices about participant preferences in a research setting while gathering evidence about various clinical practices for return of IFs. Some investigators expressed concern about the difficulty of consenting, tracking, and other logistics related to individual preferences. Further, there were concerns over liability for failure to return medically actionable results, even if refused. Although informatics systems can mask results that a participant does not want from human view, there is disagreement regarding whether such a mask obviates the "duty to warn" if such an IF exists.

Differences between adult and pediatric participants

When considering the return of IFs in the pediatric population, several issues are unique: the possibility of identifying results that are not relevant to the participant's health in childhood, such as adult-onset disease or information about carrier status; the impact of adult-onset disease findings on the parents of children being tested; and the complexity of informed consent for minors. These issues can make it more difficult to balance the principles of beneficence and nonmaleficence with the autonomy of the pediatric participant and the family. In addition, despite the natural tendency to divide disorders into pediatric- onset and adult-onset conditions, such distinctions are not always clear cut, and the typical age of onset for any given disorder does not always match the legal definition of "child" or "adult." Thus, an attempt to take into account the typical ages of onset of various conditions may greatly complicate efforts to categorize genes in an a priori fashion.

Not surprisingly, CSER sites evaluating only pediatric participant populations sometimes diverged from those CSER sites evaluating only adult participants with respect to return of results. CSER sites enrolling only adults may elect not to return IFs related to pediatric-onset disorders, even if medically actionable. Indeed, genomic IFs suggestive of a typically childhood-onset disorder, when discovered in an asymptomatic adult, may represent hypomorphic alleles that manifest at the very mild end of a phenotypic spectrum, in which case actionability is arguably reduced. Conversely, genomic results predicting adult-onset conditions may be appropriate for return to children when actionability extends to prevention of disease in family members. At the same time, the benefits of return of results must be weighed against the child's autonomy and the potential harm of the child having to bear the consequences of this information.

BCM, CHOP, and UNC are the three CSER sites that include pediatric participants. Because of the substantial risk that an unsuspecting parent might harbor the same medically actionable finding (such as a hereditary cancer syndrome) and could potentially benefit from available prophylaxis or surveillance, BCM and UNC plan to return medically actionable IFs related to adult-onset conditions to the parents of pediatric participants. By contrast, CHOP does not routinely provide adult-onset medically actionable IFs but will allow parents and/or children to elect whether or not to receive them. Although CHOP investigators are aware that adult-onset conditions might have relevance to parental health, they support the family's right "not to know" certain incidental information about their child and the family, particularly given the limitations in current understanding of the pathogenicity and penetrance of many mutations.

Conclusion

In summary, the CSER network is exploring the application of genome-scale sequencing tests through a variety of approaches to gather evidence about which genomic variants to return as IFs and under what conditions. Some CSER sites have adopted the concept of medical actionability to guide these decisions; however, the definition of actionability differs among groups. This diversity, although sometimes due to different study populations, offers a valuable opportunity to study the utility of these approaches. Here, we have outlined differences and similarities in approaches. CSER sites differ not only in the process of selecting genes for return of IFs but also in many other ways: the handling of VUSs; the timing, context, and training of the person returning the result; the ability of participants to select which results they would like returned (or not returned); the return of "nonactionable" variants; and study populations (particularly between pediatric and adult participants). The current practices of these ongoing studies highlight issues that need to be considered when offering sequencing. We anticipate that the aggregate experience of the CSER sites may inform future recommendations or guidelines on the clinical implementation of genomic testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A complete listing of secondary authors from the CSER Actionability and Return of Results Working Group is provided separately in Supplementary Table S6 online.

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Table 1

Process for determining incidental findings by CSER site

	BCM BASIC3	BWH/HMS MedSeq	CHOP PediSeq	DFCI/Broad CanSeq	UNC NCGENES	UW NEXT Medicine
Return of results committee	No ^a	Yes	Yes	Yes	Yes ^b	Yes
Participants						
Medical geneticists	Yes	Yes	Yes	Yes	Yes	Yes
Genetic counselors	Yes	Yes	Yes	Yes	Yes	Yes
Physicians (nongeneticists)	Yes	Yes	Yes	Yes	Yes	Yes
Bioethicists	Yes	Yes	Yes	Yes	Yes	Yes
CLIA-certified laboratory representatives	Yes	Yes	Yes	Yes	Yes	Yes
PhD-holding molecular geneticists	Yes	Yes	Yes	Yes	Yes	Yes
Others	Bioinformatics specialists, other specialities on consultation	Bioinformatics specialists, other scientists	Bioinformatics specialists, other scientists	Bioinformatics specialists, other scientists	Pharmacists, institutional review board chair	Other scientists
A priori list						
	No	No	Yes	Yes ^c	Yes	Yes

BASIC3, Baylor Advancing Sequencing into Childhood Cancer Care; BCM, Baylor College of Medicine; BWH/HMS, Brigham and Women's Hospital/Harvard Medical School; CHOP, Children's Hospital of Philadelphia; CLIA, Clinical Laboratory Improvement Amendments; CSER, Clinical Sequencing Exploratory Research network; DFCI/Broad, Dana-Farber Cancer Institute and Broad Institute; NCGENES, North Carolina clinical Genomic Evaluation by Next-generation Exome Sequencing; NEXT Medicine, New EXome Technology in Medicine; UNC, University of North Carolina at Chapel Hill; UW, University of Washington.

^aNo formal committee meetings held, but a laboratory-wide policy regarding threshold for reporting exists. If further discussion is needed, a subgroup or exome sign-out conference is convened.

^bSeparate committees exist for determining a priori "binning" of genes and for reviewing individual variant-level results.

^cACMG-recommended list is used as the filter for genes. Filtered variants are reviewed by a committee.

Table 2

Types of incidental findings returned by CSER site

	BCM BASIC3	BWH/HMS MedSeq	CHOP PediSeq	DFCI/Broad CanSeq	UNC NCGENES	UW NEXT Medicine
Medically actionable findings						
Returned to adults?	Yes ^a	Yes	N/A	Yes	Yes ^b	Yes ^c
Returned to children?	Yes	N/A	Yes ^d	N/A	Yes ^e	N/A
Opt out?	No	No	Yes/No ^e	Yes/No ^f	No	Yes
Non-medically actionable findings						
Carrier status?	Yes (opt in)	Yes ^g	Yes (opt in)	Yes (opt in)	Yes (opt in) ^h	No
Pharmacogenetic associations?	Yes (opt in)	Yes ^g	No	Yes ⁱ (opt in)	Yes (opt in) ^h	Yes (opt in)
Other clinically relevant variants?	No	Yes ^g	No	Yes ^j	Yes (opt in) ^h	No
Who returns results to participant?	Participating oncologist and genetic counselor	Participating physician	Ordering physician and genetic counselor	Ordering physician	Genetic counselor and medical geneticist	Genetic counselor and medical geneticist

BASIC3, Baylor Advancing Sequencing into Childhood Cancer Care; BCM, Baylor College of Medicine; BWH/HMS, Brigham and Women's Hospital/Harvard Medical School; CHOP, Children's Hospital of Philadelphia; CSER, Clinical Sequencing Exploratory Research network; DFCI/Broad, Dana-Farber Cancer Institute and Broad Institute; N/A, not applicable; NCGENES, North Carolina clinical Genomic Evaluation by Next-generation Exome Sequencing; NEXT Medicine, New EXome Technology in Medicine; UNC, University of North Carolina at Chapel Hill; UW, University of Washington.

^aParents of pediatric participants can request incidental findings.

^bIncludes pediatric-onset and adult-onset conditions.

^cSeparated into "low-penetrance variants" and "high-penetrance variants"; pediatric-onset conditions excluded.

^dSeparated into "medically actionable" vs. "immediately medically actionable" (defined as having expected presentation of symptoms within the current age category of the participant and an immediate change in medical care, including screening or intervention, that may have a significant and permanent impact on morbidity or mortality).

^eIFs deemed to be "immediately medically actionable" are not subject to preferences, but parents can decline "medically actionable" incidental findings.

^fParticipant preferences are elicited, but the committee can override preferences if the findings are immediately medically actionable.

^gThe "general genome report" includes several categories of information, including low-penetrance cardiac variants and blood groups.

^hNon-medically actionable findings are subdivided into six categories stratified by potential for psychosocial harm. Adult subjects are randomized to either a "control" group that does not receive non-medically actionable findings or an "experimental" group that chooses among the six categories.

ⁱIncludes pharmacogenomic alterations related to cancer therapeutics and other pharmacogenomic alterations.

^jCancer susceptibility-related variants.

Challenging cases

Table 3

	Would a pathogenic mutation be reported as a medically actionable incidental finding?			
	CSER site ^d			
	BCM	CHOP	UNC	UW
Comments				
<i>CYP2C19</i> genotype (metabolism of Plavix and other drugs)	Yes	No	No	No
Malignant hyperthermia (<i>RYR1</i>)	Yes	Yes ^b	Yes	Yes
Neurofibromatosis 1 (<i>NF1</i>)	Yes	Yes ^b	No	No
Familial Mediterranean fever (<i>MFEV</i>)	Yes	Yes ^b	Yes	No
Factor V Leiden (<i>F5</i>)	Yes	Yes ^b	No	Yes
Homozygous	No	No	No	No
Heterozygous	Yes	Yes ^b	No	Yes
Hemochromatosis (<i>HFE</i>)	Yes	Yes	Yes	Yes
Homozygous C282Y	Yes	No	No	No
C282Y compound heterozygosity with other mutations	Yes	Yes ^b	Yes	Yes
Gaucher disease (<i>GBA</i>)	Yes	Yes ^b	Yes	Yes
Homozygosity in a child	Yes	N/A	Yes	No
Homozygosity in an adult	Yes	Yes ^b	No	No
<i>CHEK2</i> 1100delC heterozygosity	Yes	Yes	No	No
Maturity-onset diabetes of the young (<i>HNF1A</i>)	Yes	Yes ^b	No	Yes ^c
Long QT syndrome	Yes	Yes ^b	Yes	Yes
LQT1 (<i>KCNQ1</i>)	Yes	Yes ^b	No	Yes
LQT13 (<i>KCNM5</i>)	Yes	Yes ^b	No	Yes

BCM, Baylor College of Medicine; CHOP, Children's Hospital of Philadelphia; CSER, Clinical Sequencing Exploratory Research network; *CYP2C19*, cytochrome P450 2C19; N/A, not applicable; UNC, University of North Carolina at Chapel Hill; UW, University of Washington.

^aMedical actionability of challenging cases only determined a priori by four of six CSER sites; BWH/HMS does not define variants based on actionability; all variants in this table would be reported in the MedSeq study as clinically relevant.

^b“Immediately medically actionable”—automatically released regardless of participant preference.

^cReturned for diabetic patients only because the UW project works with adults and because maturity-onset diabetes of the young is generally a pediatric-onset disorder.