The Challenge of Informed Consent and Return of Results in Translational Genomics: Empirical Analysis and Recommendations

Gail E. Henderson, Susan M. Wolf, Kristine J. Kuczynski, Steven Joffe, Richard R. Sharp, D. Williams Parsons, Bartha M. Knoppers, Joon-Ho Yu, and Paul S. Appelbaum

Introduction

Large-scale sequencing tests, including whole-exome and whole-genome sequencing (WES/WGS), are rapidly moving into clinical use.[1] Sequencing is already being used clinically to identify therapeutic opportunities for cancer patients who have run out of conventional treatment options, to help diagnose children with puzzling neurodevelopmental conditions, and to clarify appropriate drug choices and dosing in individuals. To evaluate and support clinical applications of these technologies, the National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) have funded studies on clinical and research sequencing under the Clinical Sequencing Exploratory Research (CSER) program as well as studies on return of results (RoR). Most of these studies use sequencing in real-world clinical settings and collect data on both the application of sequencing and the impact of receiving genomic findings on study participants. They are occurring in the context of controversy over how to obtain consent for exome and genome sequencing,[2] whether to return results, and the role of patient/participant preferences — controversy fueled by publication of the American College of Medical Genetics and Genomics (ACMG) recommendations for clini-

Gail E. Henderson, Ph.D., *is a Professor and the Chair of Social Medicine in the School of Medicine and an Adjunct Professor of Sociology at the University of North Carolina at Chapel Hill. She is the Principal Investigator (PI) on a grant from the National Human Genome Research Institute (NHGRI) at the National Institutes for Health establishing the Center for Genomics and Society at UNC as a Center of Excellence in ELSI Research (CEER).* **Susan M. Wolf, J.D.,** *is the McKnight Presidential Professor of Law, Medicine & Public Policy; the Faegre Baker Daniels Professor of Law; a Professor of Medicine; a Faculty member in the Center for Bioethics; and the Founding Chair of the Consortium on Law and Values in Health, Environment & the Life Sciences at the University of Minnesota. Her work on return of results and incidental findings is funded by the National Cancer Institute and NHGRI at NIH and by the Robert Wood Johnson Foundation.* **Kristine J. Kuczynski, B.A.,** *is the Project Manager in the Center for Genomics and Society, an NHGRI-funded CEER at the University of North Carolina at Chapel Hill.* **Steven Joffe, M.D., M.P.H.,** *is the Emanuel and Robert Hart Associate Professor and Vice Chair of Medical Ethics in the Department of Medical Ethics and Health Policy, Perelman School of Medicine at the University of Pennsylvania. He is a pediatric oncologist and bioethicist who has served as PI on multiple grants on return of results.* **Richard R. Sharp, Ph.D.,** *is the Director of the Biomedical Ethics Program at the Center for Individualized Medicine Bioethics Program, and Clinical and Translational Research Ethics Program at the Mayo Clinic in Rochester, Minnesota. He has led multiple NIH-funded grants on genetics and genomics.* **D. Williams Parsons, M.D., Ph.D.,** *is an Assistant Professor in the Department of Pediatrics and Department of Molecular and Human Genetics at Baylor College of Medicine, where he directs the Pediatric Center for Personal Cancer Genomics and Therapeutics. His research focuses on the clinical application of genomic technologies in pediatric cancer care.* **Bartha M. Knoppers, Ph.D., LL.B.,** *is the Canada Research Chair in Law and Medicine and the Director of the Centre of Genomics and Policy on the Faculty of Medicine, Department of Human Genetics, at McGill University, in Montreal, Canada. She founded the Population Project in Genomics (P3G) and has served as a member of the Scientific Steering Committee of the International Cancer Genome Consortium (ICGC).* **Joon-Ho Yu, Ph.D., M.P.H.,** *is a post-doctoral researcher in the Department of Pediatrics at the University of Washington, Seattle. His research interests include developing and studying culturally tailored strategies for returning genetic results from exome and whole genome sequencing through My46, a tool for individuals to manage their results and the focus of an NIH-funded research project.* **Paul S. Appelbaum, M.D.,** *is the Elizabeth K. Dollard Professor of Psychiatry, Medicine and Law at Columbia University. He is the PI of the Center for Research on Ethical, Legal & Social Implications of Psychiatric, Neurologic & Behavioral Genetics at Columbia University Medical Center, an NHGRI CEER.*

cal sequencing in 2012[3] and management of incidental findings in 2013,[4] with ensuing commentaries.[5] Indeed, debate over the ACMG recommendations on incidental findings prompted a recent amendment of those recommendations.[6]

To identify approaches used at leading U.S. institutions engaged in translating sequencing from research to clinical care, we analyzed the consent forms used in six CSER studies (funded as of early 2012), and three R01 studies in the RoR (now CSER-ELSI) Consortium. All were written before the release of the 2013 ACMG recommendations on incidental findings,[7] although some involve investigators who participated in that writing group. While prior work has analyzed consent forms in genome sequencing,[8] these nine studies aim specifically to develop best practices for clinical use.[9] By analyzing their consent forms, we sought to shed light on current approaches to consent for research on returning genomic results, broadly defined here to include both diagnostic and incidental findings from sequencing.[10] In particular, we aimed to assess the degree to which broad areas of agreement were evident.

The nine studies are among the first NIH-funded studies to consider the many practical issues associated with clinical applications of WES/WGS. Each made relatively independent decisions about how to explain sequencing, its limitations, and potential findings. Our analysis addresses four key questions: (1) What results do these studies plan to return to participants? (2) How are participant preferences taken into account in determining whether to return results? (3) What potential benefits and risks are identified? and (4) How are privacy, placement of results into the medical record, risk of re-identification, and data-sharing addressed?

Methods

The authorship team for this article is drawn from the Informed Consent and Governance Working Group within the CSER-ELSI Consortium. All six studies funded by the CSER program as of early 2012 deposited at least one example of their current consent forms in a shared Consortium Internet site. We also identified three R01s studying return of WES/WGS results. We selected one consent form from each project for full analysis, either a form intended for adults undergoing sequencing or one intended for parents/guardians giving permission for a child. For studies that used similar consent forms tailored to different disease conditions, we selected one. When studies included both adults and children, we selected the adult form. When individuals with and without identified disease conditions were included, we selected the form for affected individuals. These selection processes generated a total of nine forms for analysis.

To conduct a content analysis, four authors (PA, GH, SJ, and RS) developed a coding form based on initial review of all nine forms. Questions, codes, and quantitative and qualitative response categories were developed iteratively. Additional authors offered feedback and further modification. Development of the coding scheme benefited from the authors' deep knowledge of the ethical and legal literature on consent to genetic and genomic research. The final coding sections included open and close-ended codes for: (1) description of study design and characteristics; (2) explanation of the sequencing test and its limitations; (3) categories of results to be returned (or not); (4) processes for return; (5) description of potential benefits and risks; (6) approaches to privacy, confidentiality, de-identification, re-identification, and placing information in the medical record; (7) approaches to the use of specimens or data in other studies; and

The nine studies are among the first NIH-funded studies to consider the many practical issues associated with clinical applications of WES/WGS. Each made relatively independent decisions about how to explain sequencing, its limitations, and potential findings. Our analysis addresses four key questions: (1) What results do these studies plan to return to participants? (2) How are participant preferences taken into account in determining whether to return results? (3) What potential benefits and risks are identified? and (4) How are privacy, placement of results into the medical record, risk of re-identification, and data-sharing addressed?

(8) other permissions sought. The coding form used is available on request.

Consent forms were then coded independently by two authors (GH and KK), followed by review and resolution of discrepancies. Quantitative data were entered into an Excel spreadsheet; qualitative text data were collected for each coding section. Both data types and the original consent forms were used in analysis, with teams of two authors assigned to produce section analyses which were subsequently reviewed by all authors.

Results

Study Characteristics

The nine studies involve heterogeneous populations, including adults and/or children with cancer, cardiovascular disease, intellectual disability/neurological conditions, and unaffected individuals. Five studies include comparison or control groups, introducing additional diversity regarding the kinds of results offered, how, and to whom. There is also considerable variability in the length of the consent forms and reading level (see Table 1).

Study Purposes

The overall purpose of the studies is to understand the application of new sequencing technologies. WES is used in four studies, WGS in one, and both WES and WGS in four. The consent forms describe exome and/or genome sequencing with varying levels of detail. The most complete presentation (study #9) defines sequencing and addresses both the low likelihood of identifying diagnostic findings and the potential to identify "genetic changes related to other current or future health conditions." It describes important limitations of WES/WGS in this way: "Exome and genome sequencing do not identify all genetic alterations or disease risk. Therefore, there may be genetic alterations that will not be identified or reported. It is possible that this study will be unable to identify the cause of your or your family member's condition or other health problems.... Failure to identify a result will not guarantee that you do not have an alteration in a gene/s or a risk of developing disease in the future." All nine consent forms describe "clinical" purposes of the study; "psychosocial" purposes are described in seven, "communication" in five, and "scientific" in four. Figure 1 presents the frequency and examples of each study purpose.

1. What categories of results do these studies propose to return to participants?

The studies differ in the types of genomic results they propose to return. All return germline results; three also return somatic (tumor) results. A common approach is to list different categories of results that may be returned (or not), sometimes with illustrations for each category. For example, study #1 describes "four types of genetic information that could be examined at your request: (1) How rapidly a person's body breaks down certain medications and if a person may have a bad response to certain medications; (2) Whether a person is likely to suffer from a serious medical condi-

Figure 1

Study Purpose Domains by Study ID

STUDY DOMAINS	STUDY ID 1	2	3	4	5	6	7	8	9	Examples
Scientific	○	○	○	○	●	●	○	●	●	• "Finding new inherited mutations" • "[L]earning about newer types of sequencing approaches" • Identifying "the best methods for analyzing exome and sequencing data to identify results relevant to patients"
Clinical	●	●	●	●	●	●	●	●	●	• Determine "[w]hether sequencing results can help make treatment decisions" • ". . .[D]evelop better ways to prevent, detect, and treat [illness]" • Compare the use of sequencing with standard practice.
Psychosocial	●	●	●	●	○	●	●	●	○	• "Evaluating the impact of receiving genetic research results on research participants or their parents" • Assessing how people "understand, think about, and respond to the different types of genetic information they learn before and after this testing" • Evaluating the attitudes of physicians as well as patients and others.
Communication	○	○	●	○	●	○	●	●	●	• Discover "the best methods for educating patients and families [and physicians] about exome and genome sequencing" • "[C]ollecting feedback on genetic counseling . . . in order to improve its effectiveness in the future"

● Addressed

○ Category Not Addressed

Table 1
Study and Consent Form Characteristics

Study Characteristics	Number of Studies
Funding source	
NHGRI & NCI Clinical Sequencing Exploratory Research U01	6
NHGRI R01	3
Population enrolled	
Adults only	4
Children only	1
Adults and children	2
Adults and other family members	1
Children and other family members	1
Disease or Condition[1]	
Cancer	4
Cardiovascular	3
Intellectual disability/neurological	3
Unaffected	2
Type of sequencing	
Whole-exome	4
Whole-genome	1
Both whole-exome and whole-genome	4
Focus of sequencing	
Germline only	6
Both germline and somatic	3
Comparison group	
Yes	5
No	4
Consent Form Characteristics	**Across Studies**
Word count	
Mean	4588
Range	2917-5757
Reading level of consent form (Flesch-Kincaid Grade Level)	
Median grade level	10.8
Range	9.4-11.7

[1]Some studies focused on more than one disease condition.

tion that their doctors may be able to prevent such as cancer or sudden cardiac arrest; (3) Whether a person is likely to suffer from a serious medical condition that cannot be prevented, based on current knowledge, such as dementia or Alzheimer's disease; and (4) Whether a person carries a gene that doesn't cause any problems for them, but could lead to problems for their children or grandchildren."

Primary Diagnostic Results vs. Incidental Findings
Given debate over return of primary diagnostic results and incidental findings from clinical sequencing, we investigated the terms used to define or distinguish result types. We found that three studies distinguish primary diagnostic results from incidental findings, defined in one form as "unrelated to the primary diagnosis" (#9); one of these studies defines diagnostic information as

Table 2

Examples of Categories of Results and Number of Studies That Mention the Category

Category	Example
Preventable/ Treatable (8/9)	"These will include results related to your primary diagnosis and incidental findings that require an immediate medical action (IMA). These are findings with an immediate impact on your health or healthcare in childhood…" (#9)
	"There are 4 types of genetic information that could be examined [at the participant's request]. One of them is whether a person is likely to suffer from a serious medical condition that their doctors may be able to prevent such as cancer or sudden cardiac arrest." (#1)
Not Preventable/ Treatable (5/9)	One type of finding is…"Whether a person is likely to suffer from a serious medical condition that cannot be prevented, based on current knowledge such as dementia or Alzheimer's disease…" (#1)
	"You will also be asked if you want to learn non-medically actionable incidental information. Before you decide, we will discuss the different categories (bins) of non-medically actionable incidental information that you could learn." (#6)
	"Results related to certain untreatable adult onset disorders, such as dementia or other neurodegenerative disease." (#9)
Not Clear if Preventable/ Treatable (4/9)	"Disease Risk: Gene changes that increase your risk of getting a disease or health condition…"(#7)
	"Results that cause a difference in response to medication or a minor increased risk for common adult onset diseases such as heart disease or Alzheimer's disease…" (#9)
	"We plan to only return results to you if we feel that there is strong evidence that they may help you *manage risk of disease, predict future disease,* tell you that you carry a recessive gene that could impact a future child or help predict your response to a drug." (#2)
Pharmacogenomics (6/9)	"Genes from your normal blood cells may contain an alteration that affects the way your body handles a cancer medication. This information might mean that you need a higher or lower dose than usual for that cancer medication." (#5)
	"Gene changes that affect how your body responds to certain medications…" (#7)
	"Results that cause a difference in response to medication…" (#9)
Carrier Status (7/9)	"…an alteration for a condition (other than cancer) that you might pass on to your child. This is possible even if you do not have the condition yourself. For example, tests might show that you carry a gene alteration for cystic fibrosis that could be passed on to your child." (#5)
	"If a child has one of these kinds of mutations, he or she probably inherited it from a parent. Therefore the parents might want to be screened to see if there is a risk of having a child who has a genetic disorder. However, some people do not want to know this kind of information. Please initial below whether you would like this type of genetic information to be included in your child's exome sequencing report." (#8)
Non-medical Traits (3/9)	"it will not include other information about personal genetic traits such as eye or hair color…"(#2)
	"Results that do not have associated health problems, such as baldness…" (#9)
Negative (2/9)	"…no potentially causative variant has been identified that explains your personal and/or family history in the subset of genes that was studied…" (#6)
	"Results that indicate that you do NOT have a disease-causing change in a gene…" (#7)
Uncertain (6/9)	"Gene alterations may be found that do not have clear implications for your health…" (#5)
	"A variant has been identified in a gene associated with a genetic disorder that may explain your personal and/or family history but the clinical meaning of that variant is not known for certain." (#6)

positive, negative, or uncertain, and incidental information as medically actionable or not (#6). A fourth study (#1) recruits individuals who have had genetic testing in other studies and offers WES to "better understand the impact of return of incidental genetic test results to research participants like yourself." Three other studies use similar words such as "unexpected," "extra," and "other." Another seems to imply this idea: "We are likely to find changes in all kinds of genes, not just the genes that are related to the health condition that was looked at in the original study" (#7). Two studies *do not* make the distinction. One (#8) provides examples of potentially clinically relevant results that can be returned, including those related and unrelated to the primary disease. The other (#3) enrolls "medically-educated staff" and provides little detail about what types of health-related results might be returned.

Categories of Results

We identified eight categories of results described in these consent forms: related to health and (1) preventable/treatable, (2) not preventable/treatable, or (3) not clear if preventable/treatable, (4) pharmacogenomics, (5) carrier status; and more generally, (6) non-medical traits, (7) negative results, and (8) uncertain results. The number of results categories ranged from one to eight per study, reflecting considerable diversity in study design and population. Table 2 shows studies offering each results category, with examples. We also found variation in how consent forms address CLIA-certification of results. Four forms state that only results from a CLIA-certified laboratory will be returned; two say that some results will be from a CLIA-certified lab, but others will not; one is unclear about whether results will be from a CLIA-certified lab; one states results will *not* be from a CLIA-certified lab; and one does not address the issue.

2. To what extent are participant preferences taken into account in determining whether to return results?

We used four codes to identify whether and on what basis each type of result is returned: (1) the result will be returned, (2) participant preferences determine whether the result will be returned, (3) the result will not be returned, and (4) return of this type of result is not addressed. Figure 2 describes the variability we found in categories of results mentioned and the studies' plans for returning results, including the role of participant preferences.

As noted, not all studies mention all types of results and there is variability in the role of participant preferences. In two studies (#1, 3), participant preferences determine what is returned in *all* categories. A third study (#7) follows suit, except for "non-medical traits" and "negative" and "uncertain" results, which are not returned. In contrast, participant preferences play *no* role in one study (#2). Another study (#4) only mentions results that are "related to health and preventable/treatable," and return depends solely on whether they are related to a primary diagnosis. Studies #6, #8, and #9 also return results "related to health and preventable/treatable" regardless of participant preferences; however, modes of return for other identified categories vary.

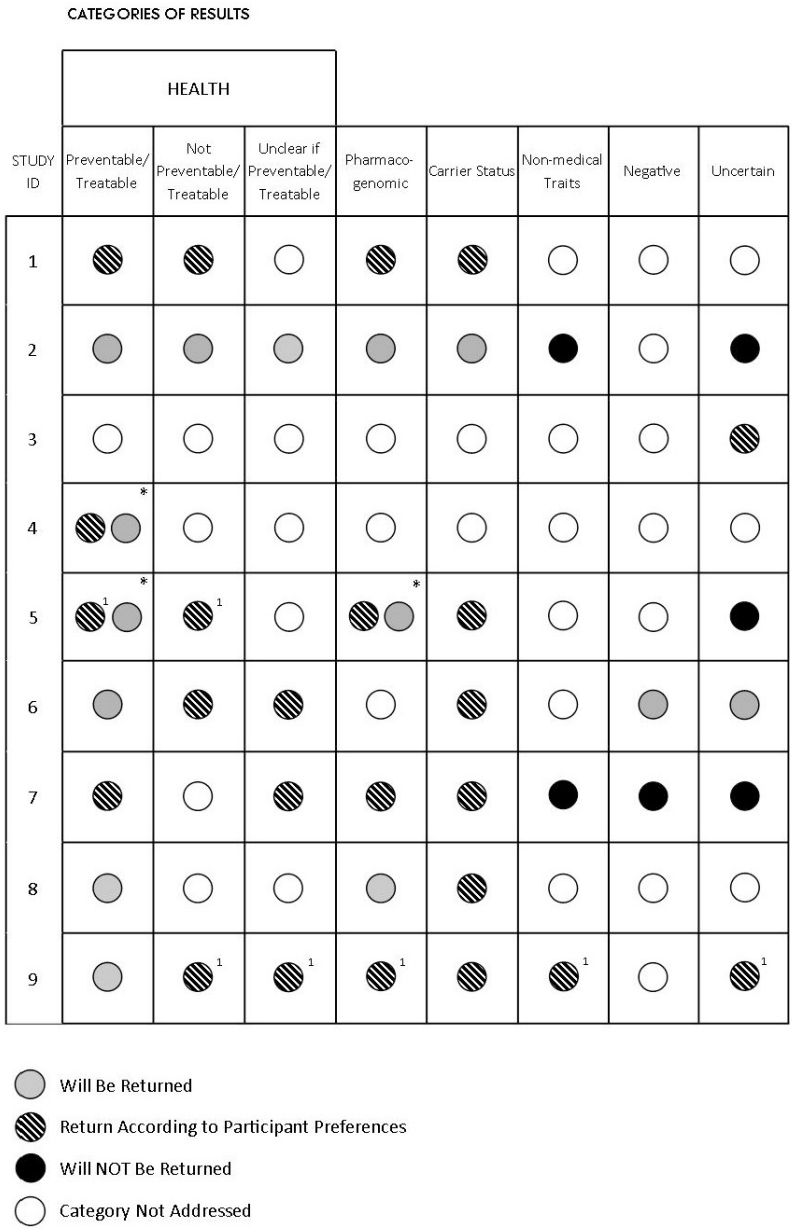
Two studies introduce additional complexity about the role of participant preferences. Study #5 mentions five types of results, with clear return policy for "carrier status" and "uncertain" results, but mixed information regarding return of non-diagnostic information that investigators judge to be urgently medically actionable (i.e., "[W]e may tell you and your doctor information about this alteration even if you have not previously given us your permission to do so.") Conversely, investigators may decide *not* to return certain results that participants have requested: study #9's consent form states "receiving results of incidental findings without immediate medical impact is voluntary," yet also lists types of findings that the study "may not release."

Figure 2 illustrates three observations about return of results. First, for results "related to health and preventable/treatable," returning without consulting participants about their preferences is common (6/8 studies). This may be because these studies are seeking diagnostic results for affected individuals whose preferences for results are reflected in their consent to participate in the study. In study #4, for example, "preventable/treatable" diagnostic results are returned without consulting participants, whereas "preventable/treatable" *incidental* findings are returned only according to participant preferences. In contrast, in two studies (#1, 7), participant preferences govern return of *all* "preventable/treatable" results.

The second finding is that more varied approaches to the role of participant preferences are evident for categories other than "related to health and preventable/treatable." This includes results "related to health but not preventable/treatable" (e.g., Alzheimer's or neurodegenerative conditions); when "preventable/treatable" is unclear (vague statements about learning disease risk with no additional information); and results related to pharmacogenomics (depending in part on whether these are related to the primary diagnosis). Return of "carrier status," in contrast, is typically offered only per participant preferences (6/7 studies).

Figure 2

Study ID by Categories of Results and Mode of Return When Offered



*In three instances, the mode of return required two codes assigned to one "cell'." To illustrate, in study #5, the "preventable/treatable" cell for study #5 is assigned both "results will be returned" and "participant preferences will determine whether or not the result will be returned." In this case, "result will be returned" refers to results related to the main diagnosis that are "preventable/treatable," while the latter refers to return of incidental findings that are also "preventable/treatable."

[1]Override. This describes instances where the consent form states that the participant has the option to choose the results returned, but then later states that the study may override the participant's decision with respect to certain kinds of results. Study #5 notes that investigators may override participant preferences regarding non-diagnostic information when information is considered urgently medically actionable. Studies #5 and #9 also describe an override in the opposite direction, in which participants may choose certain types of non-medically actionable incidental findings yet investigators may decide not to release them.

Table 3
Potential Benefits and Risks of Participation Identified in 9 Consent Forms

Potential Benefits:	
Benefit to society	7
Information on risk of another disease [other than primary condition]	7
Information on cause of condition	4
Information on reaction to medications	4
Information for reproductive decision-making	4
Identify treatment for your condition	3
Information on prognosis	2
Other (listed on only one form each)	6
Potential Risks:	
Blood draw risks	9
Emotional & psychological distress for self and family	9
Genetic discrimination	8
Loss of privacy	8
Unknown risks	7
Tension among family members	5
Potential for re-identification	4
Emotional & psychological distress from discussing personal things	3
Potential for inaccurate information	3
Emotional & psychological distress from uncertainty	2
Financial costs downstream	2
Other (listed on only one form each)	6

Third, some studies explicitly state that they will not return results concerning "non-medical traits," "negative," and "uncertain" findings. "Uncertain" findings show the greatest variation: they *will not* be returned in three studies (#2, 5, 7); *will* be returned in one (#6), which includes "uncertain" results as one of three diagnostic possibilities; and they are returned *based on participant preferences* in two (#3, 9).

3. How are potential benefits and risks of participating in the study described?

Table 3 summarizes how studies describe potential benefits and risks of participation. Seven potential benefits are listed on two or more forms; six "other" benefits are listed on one form each. Seven studies mention benefit to society (i.e., creation of generalizable knowledge); one mentions this as the only benefit. Twelve possible risks of harm are listed on two or more forms; six "other" risks are mentioned on one form each. All but one of the forms mention both genetic discrimination and loss of privacy as risks of participation.

4. How are privacy, placement of results into the medical record, risk of re-identification, and data-sharing addressed?

The volume of information generated by sequencing and the heightened potential for re-identification create special challenges for privacy and confidentiality.[11]

Privacy

As shown in Table 3, all but one of the forms mention risks of genetic discrimination and loss of privacy. Most reference potential discrimination by insurers and employers, despite the partial protection offered by the federal Genetic Information Nondiscrimination Act (GINA), which addresses employment and health insurance but does not address other forms of insurance such as disability and life insurance. In addition, five forms refer directly or indirectly (through men-

tion of "protected health information") to the protections afforded by HIPAA. No forms refer to additional privacy protections afforded by law. Five forms note that the investigators have applied for or obtained a Certificate of Confidentiality.

Information in the Medical Record

Eight forms address placing genetic information in the participant's medical record. Five CSER studies state that results will be placed in the medical record, while the sixth leaves the choice to participants. Among the five, there is variation. One states, "all of your reports will be placed in your medical record" (#2), while others are selective about the kind of information; for example, one (#9) includes "Only validated results that are directly relevant to your care at [Institution]" and excludes "Other incidental findings identified solely for the purpose of this research study, including results for adult-onset disease and carrier states." Of the three RoR studies, one has an optional plan, one does not address the issue, and one (#3) states, "No genetic test results will be put into your medical record as part of this study," yet cautions "if you share these results with a health care provider, the result may be included in that providers [*sic*] record."

Risk of Re-identification

Four forms explicitly address potential re-identification as a risk of participation. One states, "... in the future, people may develop ways to allow someone to link your genetic or medical information in these databases back to you" (#2).

Data-Sharing

Seven consent forms address storage and the use of data in other studies. Four of these present this as part of the agreement to participate, and three have separate permissions.

Discussion

This analysis of consent forms from the CSER-RoR projects illustrates how investigators are grappling with consent-related challenges inherent in new sequencing technologies. These challenges include providing clear descriptions of the kinds of expected findings, which findings may be returned, the role of participant preferences, and whether results will be placed in the medical record. At this early stage in the use of sequencing, there is considerable heterogeneity in the responses to these challenges. Though NHGRI provides helpful guidance on informed consent for genomic research generally,[12] exploration of multiple models for consent to clinical sequencing is clearly under way.

This analysis of consent forms from the CSER-RoR projects illustrates how investigators are grappling with consent-related challenges inherent in new sequencing technologies. These challenges include providing clear descriptions of the kinds of expected findings, which findings may be returned, the role of participant preferences, and whether results will be placed in the medical record. At this early stage in the use of sequencing, there is considerable heterogeneity in the responses to these challenges. Though NHGRI provides helpful guidance on informed consent for genomic research generally, exploration of multiple models for consent to clinical sequencing is clearly under way.

All of these studies offer to return at least some findings to participants. However, the diversity regarding the types of information that may be returned and the role of participant preferences is notable. No category of result is consistently returned in all studies and several categories are mentioned in just a few studies. Moreover, the degree to which return of results depends on participant preferences varies significantly, ranging from studies that determine in advance what will be returned to studies that return only the categories of results requested by participants. In one study (#2), no category of potential finding was governed by participant preference, while in another study (#1), all categories were. A wide range of approaches to return of results in sequencing research was documented in a 2011 study,[13] and it is striking to see that there remains so little convergence of approaches, as sequencing is rapidly evolving.[14] On the other hand, we caution that this lack of convergence may be less a sign of disagreement over "best" approaches than a reflection of the diversity of study designs exploring sequencing.

Indeed, these studies may shed light on the controversial question of whether some findings should

be returned regardless of participant preferences.[15] This question has been intensively debated since ACMG's 2013 recommendation that whenever clinical sequencing is performed, a "minimum list" of 56 extra genes should be analyzed for incidental findings that are likely to be medically actionable, with no patient option to decline that additional analysis.[16] Five of the studies we analyzed are exploring return of specific categories of medically actionable results regardless of participant preferences, although these results are generally diagnostic findings, in contrast to the incidental findings addressed by the ACMG recommendations. Approaches to the return of medically actionable incidental findings unrelated to diagnosis are more mixed: some studies return them without consulting participant preferences, whereas others only return them based on participant preferences. Some studies in our sample are returning results regardless of participant preferences even when not in the medically actionable, "preventable/treatable" category. This wide range of approaches to the role of participant preferences should yield data to inform best practices. However, the diversity of approaches suggests the need to address underlying societal norms and professional values that motivate offers of different types of results with varying attention to participant/patient preferences in both research and clinical settings. As noted above, ACMG has now modified its approach to incidental findings in clinical sequencing, recommending that patients be allowed to opt out of the analysis for medically actionable incidental findings.[17]

Our analysis revealed considerable variation in potential benefits and risks described (Table 3). In addition, we found varying approaches to data-sharing and the potential for re-identification of genomic results. We also found a range of approaches to whether genomic information would be placed in the participant's medical record, which information, and the role of participant preferences. This points to the challenging questions of how to integrate genomics into the medical record, specifically the electronic health record, and whether placing incidental findings in the medical record raises somewhat different issues than recording diagnostic results and may require separate consent.[18]

Given the range of approaches we found across a spectrum of results categories, our coding tasks were complex and challenging. The coding categories emerged from reading all nine consent forms. Coding became difficult when a consent form addressed multiple categories of results, took different approaches to the role of participant preferences in returning different categories of results, or presented unclear or conflicting information about categories or preferences. These features made it challenging to identify how different categories of results were handled in some studies. Indeed, two studies have language in different sections of the consent forms that suggests circumstances in which the investigator can override participant preferences, as noted above. These provisions may have been motivated by investigators' desires to preserve their discretion with regard to decisions about return, given uncertainties at the inception of projects about what types of results might be encountered or what policies might be formulated by return-of-results committees. Whatever their origin, conflicting messages are likely to be at least as difficult for research participants to interpret as they were for our team. Complicating this further, no form reaches the often-recommended eighth-grade level of reading ease,[19] though none exceeds the level expected of a high-school graduate.

This analysis has limitations. We assessed consent forms from a small number of studies, designed early in the process of clinical translation of WES and WGS. Forms from three additional CSER studies funded subsequent to the completion of our data analysis were not analyzed here, and a number of other research groups are now engaged in or planning sequencing studies. Indeed, several studies included here have since modified or added consent forms that might alter our initial coding results. Hence, our results represent a snapshot in time, reflecting evolving approaches. Our analysis focuses exclusively on the content of consent forms, which is only a part of the consent process. Thus, the forms may not fully reflect more detailed procedures specified in study protocols, to which we did not have access. We did not analyze supplemental oral communication or how these forms are used in practice, though in some cases our familiarity with the studies in question allowed us to clarify uncertain study design information. Some investigators in the studies whose forms are analyzed here have indicated that their study uses instruments beyond the consent form (such as an educational DVD or a separate questionnaire) to communicate further with participants about specific categories of results and solicit preferences; those additional instruments were not part of our coding. Lastly, coder misclassification may have occurred, though all forms were coded by multiple individuals with disagreements resolved, results discussed by our broader author group, and when questions arose, coding decisions checked against the original consent forms.

Notwithstanding these limitations, our findings may be helpful in suggesting ways in which consent forms for WES/WGS studies can be improved, and potentially consent forms for clinical sequencing as

well. Based on our review, we offer the following recommendations: (1) define WES/WGS and address its limitations; (2) describe the processes and challenges of expert review that determine the results to be returned, and the role of CLIA certification; (3) describe possible results related to diagnostic or incidental findings (if that distinction is appropriate for the context), state the likelihood of producing such results, and indicate whether they are related to conditions that are preventable/treatable; (4) specify the meanings of positive, negative, and uncertain results; (5) describe the role of patient or participant preferences in return of results; (6) specify the potential benefits and risks of participation (including benefit to society, when sequencing is performed in the research context); and (7) consider the many facets of privacy, placing findings in the medical record, de-identification, data-sharing, and risk of re-identification. These recommendations, based on comparing and analyzing the consent forms in this study, can serve as a checklist to help identify gaps and resolve ambiguities in consent forms for sequencing. Our recommendations go beyond the general guidance offered by NHGRI on seeking consent to genomic research[20] by focusing on key elements needed in consent to sequencing, such as clarity about the limitations of WES/WGS, a description of the processes that will be used to determine which results to return, and the meaning of positive, negative, and uncertain results.

Selecting among approaches to return of results and incidental findings will depend on a variety of factors, including research population and study aims. It will also depend on normative positions concerning the entitlement of participants to determine which results they will receive, and empirical findings regarding the impact of individual genomic results and incidental findings on participants' psychological well-being, health-related practices, and medical care. The wide variation in practices revealed by our analysis highlights the diverse strategies currently being used to address the practical challenges of genomic sequencing of study participants and patients. As researchers and clinicians gain experience with new forms of genomic analysis, it will be important to develop evidence-based and normatively sound points of consensus on best practices for informed consent and return of both diagnostic results and incidental findings in exome and genome sequencing.

Acknowledgements

Preparation of this article was supported in part by NIH grants P50HG004488 (Henderson), U01HG006487 (Henderson), R01CA154517 (Wolf), Robert Wood Johnson Foundation grant 69763 (Wolf), U01HG006492 (Joffe), R01HG004500 (Sharp), P50HG003390 (Sharp), U01HG006485 (Parsons), R21HG00612 (Knoppers), Genome Canada/Genome Quebec (Knoppers), R01HG006618 (Yu), R21 HG006596 (Appelbaum), P50HG007257 (Appelbaum). Opinions expressed in this manuscript are those of the authors and do not reflect the official position of the National Institutes of Health or other funding agencies or institutions with which the authors are affiliated. We wish to thank the Principal Investigators of the CSER and R01 grants who allowed their consent forms to be used in this study. Some raised important points of clarification about their studies, but were not otherwise involved in any aspect of the analysis we report in the paper.

References

1. T. A. Manolio et al., "Implementing Genomic Medicine in the Clinic: The Future Is Here," *Genetics in Medicine* 15, no. 4 (2013): 258-267.
2. See ACMG Board of Directors, "Points to Consider for Informed Consent for Genome/Exome Sequencing," *Genetics in Medicine* 15, no. 9 (2013): 748-749; C. Ayuso et al., "Informed Consent for Whole-Genome Sequencing Studies in the Clinical Setting: Proposed Recommendations on Essential Content and Process," *European Journal of Human Genetics* 21, no. 10 (2013): 1054-1059; T. Caulfield et al., "Research Ethics Recommendations for Whole-Genome Research: Consensus Statement," *PLoS Biology* 6, no. 3 (2008): e73; G. E. Henderson, "Is Informed Consent Broken?" *American Journal of the Medical Sciences* 342, no. 4 (2011): 267-272; C. Kronenthal, S. K. Delaney and M. F. Christman, "Broadening Research Consent in the Era of Genome-Informed Medicine," *Genetics in Medicine* 14, no. 4 (2012): 432-436; A. L. McGuire and L. M. Beskow, "Informed Consent in Genomics and Genetic Research," *Annual Review of Genomics and Human Genetics* 11 (2010): 361-381; K. E. Ormond et al., "Challenges in the Clinical Application of Whole-Genome Sequencing," *The Lancet* 375, no. 9727 (2010): 1749-1751; Presidential Commission for the Study of Bioethical Issues, *Privacy and Progress in Whole Genome Sequencing*, October 2012, *available at* <http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf> (last visited July 30, 2014); R. R. Sharp, "Downsizing Genomic Medicine: Approaching the Ethical Complexity of Whole-Genome Sequencing by Starting Small," *Genetics in Medicine* 13, no. 3 (2011): 191-194; S. B. Trinidad et al., "Informed Consent in Genome-Scale Research: What Do Prospective Participants Think?" *AJOB Primary Research* 3, no. 3 (2012): 3-11.
3. ACMG Board of Directors, "Points to Consider in the Clinical Application of Genomic Sequencing," *Genetics in Medicine* 14, no. 8 (2012): 759-761.
4. R. C. Green et al., "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," *Genetics in Medicine* 15, no. 7 (2013): 565-574; American College of Medical Genetics and Genomics (ACMG), "Incidental Findings in Clinical Genomics: A Clarification," *Genetics in Medicine* 15, no. 8 (2013): 664-666.
5. See, e.g., W. Burke et al., "Recommendations for Returning Genomic Incidental Findings? We Need To Talk!" *Genetics in Medicine* 15, no. 11 (2013): 854-859; J. E. McEwen, J. T. Boyer and K. Y. Sun, "Evolving Approaches to the Ethical Management of Genomic Data," *Trends in Genetics* 29, no. 6 (2013): 375-382; A. L. McGuire et al., "Point-Counterpoint. Ethics and Genomic Incidental Findings," *Science* 340, no. 6136 (2013): 1047-1048; Presidential Commission for the Study of Bioethical Issues, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*, December 2013, *available at* <http://bioethics.gov/sites/default/files/FINALAnticipate-Communicate_PCSBI_0.pdf> (last visited July 30, 2014); S. M. Wolf, G. J. Annas, and S. Elias, "Point-Counterpoint. Patient Autonomy and Incidental Findings in Clinical Genomics," *Science* 340, no. 6136 (2013): 1049-1050.
6. American College of Medical Genetics and Genomics (ACMG), *ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results*, April 1, 2014, *available at*

<https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf> (last visited July 30, 2014).
7. See Green et al., *supra* note 4.
8. C. Allen and W. D. Foulkes, "Qualitative Thematic Analysis of Consent Forms Used in Cancer Genome Sequencing," *BMC Medical Ethics* 12, no. 1 (2011): 14.
9. See National Human Genome Research Institute (NHGRI), "Clinical Sequencing Exploratory Research," *available at* <http://www.genome.gov/27546194> (last visited July 30, 2014).
10. See S. M. Wolf et al., "Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets," *Genetics in Medicine* 14, no. 4 (2012): 361-384.
11. See B. M. Knoppers, M. H. Zawati and E. S. Kirby, "Sampling Populations of Humans Across the World: ELSI Issues," *Annual Review of Genomics and Human Genetics* 13 (2012): 395-413.
12. National Human Genome Research Institute (NHGRI), "Informed Consent for Genomics Research," *available at* <http://www.genome.gov/27026588> (last visited July 30, 2014).
13. See Allen and Foulkes, *supra* note 8.
14. See Manolio et al., *supra* note 1.
15. See Green et al., *supra* note 4.
16. *Id*., at 567.
17. See ACMG, *supra* note 6.
18. See J. L. Kannry and M. S. Williams, "Integration of Genomics into the Electronic Health Record: Mapping Terra Incognita," *Genetics in Medicine* 15, no. 10 (2013): 757-760; R. Hazin et al., "Ethical, Legal, and Social Implications of Incorporating Genomic Information into Electronic Health Records," *Genetics in Medicine* 15, no. 10 (2013): 810-816.
19. M. K. Paasche-Orlow et al., "Readability of Consent Form Templates: A Second Look," *IRB* 35, no. 4 (2013): 12-19.
20. See NHGRI, *supra* note 12.