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Cases in Precision Medicine: Should You Participate in a Study Involving Genomic Sequencing of Your Patients?

Paul S. Appelbaum, MD[1], **Deborah F. Stiles, JD**[2], **Wendy Chung, MD, PhD**[3]

[1]Columbia University Irving Medical Center and New York State Psychiatric Institute

[2]Office of the Executive Vice President for Research, Columbia University

[3]Columbia University Irving Medical Center

Case Example

Researchers from the medical school with which your general internal medicine practice is affiliated have asked you to participate in a study of the value of genome sequencing in the clinical care of individuals with no known genetic disease. Your participation would involve recruiting your adult patients to join the study, obtaining consent from patients who agree to participate, drawing a blood sample for the genomic testing, returning the results of the genomic testing to your participating patients, and being a member of the team that will assess the clinical value of the data for clinical practice. The opportunity to participate in a study that will help define the role of genomic testing in clinical care is intriguing, but you would like more information before agreeing to participate. What questions should you ask the researchers?

Introduction

Notwithstanding the growing use of genetic tests in clinical medicine in recent years for both diagnostic and predictive purposes, the role of genomic screening—including exome and genome sequencing—in the care of generally healthy populations is less clear. (1) Thus, the study being planned in this case targets an important issue for clinical medicine. However, the large amount of data generated with genomic screening raises challenges for the clinician. A physician might reasonably be concerned about the time and effort required to recruit and explain the study to patients, understand and interpret the genetic results for patients, and recommend possible follow-up care, and whether compensation will be provided for his/her time and how the physician's contribution will be acknowledged.

Decisions about participation in clinical research should be made thoughtfully, particularly because integration of genomic medicine into clinical care, including disclosing results of genomic sequencing to patients and research participants, is still a work in progress. However, sufficient experience now exists to provide guidance to clinicians considering participation in genomic research studies as to what questions to ask the research team.

Corresponding author: Dr. Paul Appelbaum, NY State Psychiatric Institute, 1051 Riverside Drive, Unit 122, New York, NY 10032-8630; 646-774-8630; psa21@columbia.edu.

In what laboratory or laboratories will the study conduct its genomic testing?

Because the results of the genomic testing in our study may inform the internist and enrolled patients of potential clinical concerns, it is important that the internist confirm with the research team where the generation of the genomic sequences and the analysis of the data will be performed. To ensure the accuracy and analytic validity of laboratory test results, U.S. laboratories providing information that may be used in the diagnosis or treatment of disease are subject to the Clinical Laboratories Improvement Amendments of 1988 (CLIA). (2) CLIA requires that all such laboratories be certified unless they are exempt or excepted. Many researchers do not use CLIA-certified laboratories because the certification requirements result in higher costs or because the desired analyses are not yet available in CLIA-certified facilities. Given that the explicit purpose of the study in this case is to return genomic information and examine its impact on medical care, the internist will want to be sure that the testing is in fact being performed, or the results confirmed, in a CLIA-certified laboratory.

What genomic test results and associated information will the study provide?

Genomic screening can identify a large number of variants of potential medical relevance. They differ in the seriousness of the resulting condition and the degree of disease risk; age of onset; availability, cost, burden, and timing of preventive or therapeutic interventions; and opportunity for reversibility. Given the need to balance costs associated with returning findings with the value of the information to clinicians and patients, a variety of criteria have been suggested for deciding which results should be offered for return. (3) A 2015 position paper by the American College of Medical Genetics and Genomics (ACMG) recognized the broad utility of genomic testing, urging that decisions about such testing “should take into account effects on diagnostic or therapeutic management, implications for prognosis, health and psychological benefits to patients and their relatives, and economic impact on health-care systems.” (4, p.505) In 2018, the National Academies produced a report on return of results from research that suggested decisions need to be made on a case-by-case basis, balancing the value to participants of returning particular findings against the feasibility of disclosure, including the costs in time and resources. (5)

The value of genomic results to patients can be clinical or personal. The clearest reasons for offering to return results are when they are “clinically actionable”—i.e., results that may guide decisions on preventive interventions or treatment, especially for serious, life-threatening or life altering conditions. For example, the ACMG recommended in 2013 that known and expected pathogenic variants in 56 (later revised to 59) genes associated with potentially life-threatening conditions be available for return in clinical testing as secondary findings, regardless of the reasons that genomic testing had originally been ordered. (6) Some examples of clinically actionable variants and preventive interventions include mutations on the *BRCA1* gene associated with hereditary breast/ovarian cancer (breast cancer screening, mastectomy, oophorectomy); the *MLH1* gene associated with hereditary

nonpolyposis colon cancer (colonoscopy, prophylactic surgery); and the *KCNQ1* gene associated with long QT syndrome (beta blocker, avoidance of QT-prolonging medication). In addition, pharmacogenomic information can help identify individuals at risk for reduced therapeutic response or toxicity when given standard doses of particular medications. However, there remains considerable diversity of views about which variants should be returned and under what conditions. (7)

Personal value can take a variety of forms. Genomic testing can provide information about carrier status for autosomal recessive diseases that, although unlikely to impact a person's own health or medical care, may be of importance for reproductive planning. In addition, genomic results may inform other aspects of life planning, such as purchasing life or long-term care insurance, retirement plans, career choices, or choices about residence. Even when there are no practical consequences, genomic results can offer people a sense of greater knowledge about themselves, including ancestry. (5)

Although considerable concern has been expressed about adverse psychological effects from receiving results that have serious health implications or uncertain significance, most studies to date have failed to report more than transient test-related distress. On average, neither long-term anxiety nor depression has been found to increase after testing, although there may be considerable individual variability. (8) However, these data tend to come from participants who sought genetic testing, received a single result, and were afforded pre-test and post-test genetic counseling. Whether adverse responses are more likely to accrue in other situations is unclear. (9). Risks associated with misunderstanding test results and their implications can include inappropriate action (e.g., prophylactic surgery) or inaction (e.g., failure to get proper screening). Social consequences, including stigmatization, the economic impact of anticipated changes in earning potential, and adverse effects on relationships with others, including family members, may also occur. (5)

Given that there may be both clinical and personal utility to participants in returning genomic results, and in light of the reassuring findings about the infrequent occurrence of negative psychological effects, research studies are increasingly planning to offer to return at least some results. Investigators often rely on the ACMG list of secondary findings from clinical testing or some modified version thereof to identify actionable results to return. Many studies show that participants have high levels of interest in genetic results, although there is some variability across specific results. (10) It is therefore important to understand "what participants in the study would find to be of value and what their preferences are for receiving results after the benefits, risks and trade-offs have been discussed." (5, p.154) The best way to reach this understanding is through the consent process.

Will participants have a choice about the type of results they want the researchers to provide to them? If so, at what point in the study will they make this decision?

There is a consensus that genetic findings should not be returned without a participant's consent. Genomic research adds considerable complexity to the standard consent

requirements because, in addition to the usual components of a research consent, the discussion will entail providing information about the nature and likelihood of the findings, the meanings of positive, negative, and uncertain findings, the benefits and risks associated with the return of results, and issues of privacy and confidentiality, data use and security, and relevance to family members. (11) Ascertaining participants' preferences for return of results can be facilitated by grouping categories of results into "bins" (12), e.g., medically actionable findings, non-actionable findings that may have implications for life-planning, findings with reproductive implications, pharmacogenetic findings, etc. How many of these categories are offered to participants and the precise content of the bins will depend on the balance of value and feasibility described above. Participating physicians will need to consider that allowing patients to refuse return of results could mean that potentially life-saving information will not be returned to them. Advance discussion with the research team about how this situation will be handled could be extremely helpful if such situations arise.

One approach to reducing the complexity of the initial consent process is staged consent. Under this model, at the outset of the study, participants are informed that results may be available and, if relevant, they will be reapproached at that time to determine whether they would like to receive them. Deferring consent to a time immediately proximal to return of results may reduce the effort required to obtain consent if a small fraction of participants are expected to receive results and allow a more focused discussion and decision process. It also better allows patients to take their current clinical and life situations into account in framing their preferences. (13) On the other hand, recontacting participants for another consent could be costly and burdensome, and recontact itself can reveal unwanted information. Given these complexities, a growing number of resources are available to assist the development of a consent process, such as the Multi-Regional Clinical Trials Center's toolkit that contains guidance for informed consent documents, checklists and model language, as well as case studies. (14)

How will the researchers help you understand the results of study-related genomic tests that you are expected to discuss with your patients?

Results from genomic testing are embodied in laboratory reports that identify the variant(s) in question. Although not all laboratories agree in their variant interpretation, most use the classification developed by the ACMG and the Association for Molecular Pathology. (15) If a particular variant has sufficient evidence to be associated with a medical condition, the variant is classified as "pathogenic." However, when evidence is strongly suggestive but insufficient to be definitely associated with a medical problem, it is classified as "likely pathogenic." Because likely pathogenic variants are not definitive, they can either be upgraded to pathogenic or downgraded to being of uncertain significance as new evidence becomes available. Clinically, pathogenic and likely pathogenic variants are usually treated the same—as if they are disease causing—and clinical management is tailored accordingly. (16)

A variant is designated as "variant of uncertain significance" ("VUS") when (a) the effect of the variant on gene function is not known and (b) there are insufficient data to confirm that

the variant is associated with disease risk or is benign. (16) Clinicians generally are advised not to use a VUS for clinical decision-making. In many genomic screening studies, VUS are not routinely reported. Also, variant interpretation may change over time, as new information becomes available. Many genetic testing laboratories will routinely send an amended report to the physician who ordered the test when a variant is reclassified in a way that would change clinical management. (16) Our internist should inquire whether this study will reclassify variants and issue revised reports over time.

If there is evidence that the variant is not associated with a disease condition, a variant is called “likely benign” or “benign” and is not generally reported. Of note, because of the limits of genetic knowledge and technology, the absence of pathogenic or likely pathogenic findings does not eliminate the possibility of a genetic cause or increased genetic risk for a medical condition due to other genetic causes that were not known or included in the test. Therefore, a negative genetic test does not eliminate the possibility of an increased genetic risk.

Once the results are in hand, the physician will be faced with the challenge of assessing the clinical implications and possible clinical actions. This task is complicated by the variable effects and incomplete and age/sex dependent penetrance of mutations in genes. A growing number of resources and decision-support tools are being developed to assist in understanding the results, such as OMIM (17), ClinVar (18), GeneReviews (19), and National Comprehensive Cancer Network (NCCN) guidelines. (20) Publications such as the Guide to Interpreting Genomic Reports: A Genomics Toolkit (16), developed by a NIH-funded consortium, have been created to assist clinicians. However, busy physicians may lack the time and expertise to seek out and understand the information in these resources. Thus, it would be critical for the internist in our case to have access to a geneticist or a genetic counselor who can provide consultation for the physician and, if needed, counseling for patients.

How can you best communicate genomic test results to patients to maximize understanding and minimize potential negative consequences, such as unwarranted follow-up testing or unnecessary stress?

Physicians receiving results from genomic testing will need to communicate the results in a manner that facilitates patients’ understanding of the findings and their implications. Strategies developed for health communications in general can be helpful here, such as identifying a single takeaway message to emphasize, often focused on the action that patients should take or the fact that no action is indicated. Patients may need particular assistance with the inherent uncertainty of the findings or their implications. Often, educational materials can be helpful during and after a disclosure session, including educational videos, visual aids explaining inheritance patterns and the limitations of testing, carrier status handouts, and concise summaries of key findings in a bulleted format. (8)

A recent article concluded that “contextualizing and communicating research results in a manner understandable to laypersons is a daunting task… [R]esearch participants have a

spectrum of literacy, speak multiple languages and have variable states of emotion and cognition…suggesting that materials for return of results should be tailored to the individual." (21, p.436) The authors suggest that partnering with participants' clinicians is a helpful course of action and "engaging clinicians in developing policies for the return of results may help identify creative and practical approaches." (21, p.436) There is thus potentially an important role for the internist in our case to play in assisting the research team in designing the effective return of results.

Will the study provide patients access to expert genetic consultation should they want or require it after obtaining genomic test results?

Even the most skilled communicators may lack the underlying knowledge to respond to patients' questions or the ability to help them sort through possible approaches to mitigating risk. In these cases, referral to a genetic counselor can be helpful. Genetic counselors have counseling skills and an understanding of genetic disorders that, combined with a familiarity with laboratory methods, permits them to communicate knowledgeably and effectively with patients. Although the number of genetic counselors is inadequate to serve the increasing number of patients undergoing genomic testing, a number of studies have shown that education and counseling can be provided effectively via video or telephonic links and that using genetic counselors to supplement online resources can increase the efficiency of the counseling process. (5) If not provided by the study, the National Society of Genetic Counselors has patient and provider resources on its website, including a searchable tool to "find a genetic counselor near you." (22)

Anticipating Greater Clinical Use of Genomic Testing

Most genetic testing of adults today, even when sequencing technologies are employed, focuses on single genes or a panel of genes, not the entire exome or genome. Moreover, with rare exceptions, genomic screening of healthy populations is limited to research settings. However, the principles outlined above can be applied to genomic testing in clinical contexts, including approaches to determining which results should be returned, how consent can be obtained, and how the results and their implications can best be communicated to patients. Physicians can ready themselves for that process by improving their own genomic literacy and skills in communicating complex and uncertain information.

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Key Points

- Physicians who are considering participation in genomic screening studies should carefully consider the implications for their practices and their patients.
- Because genomic studies can identity a large number of variants with clinical or personal value for patients, physicians should determine which results will be returned and how they are likely to affect patients.
- Provisions should exist for obtaining consent from research participants for return of results. Informational tools exist to help participants through the process of deciding which results to receive.
- Given the complexity of genomic results, including variable penetrance, the research study should provide support to physicians to understand the results and their implications for patients.
- Physicians should be prepared to communicate results in a manner that facilitates patients' understanding of the findings and their implications. The communication process should be tailored to the needs of the individual patient.
- Engaging genetic counselors in helping patients understand the implications of genomic findings can be helpful, as they have a scientific understanding of genetic disorders, are experienced in dealing with patients, and are trained in counseling skills.