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

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Internists and other physicians may be asked to participate in research studies that include genomic screening of their patients. Because genomic studies can identify many variants with potential clinical or personal implications, physicians should carefully consider the effect of participation on their patients, as well as the time and effort needed for the physicians to interpret the results and decide how best to use the information. Among the questions they will need to explore is whether testing will be done in a laboratory that is certified under the Clinical Laboratory Improvement Amendments and authorized to generate results for clinical purposes. Physicians should also determine which results will be returned and how these results are likely to affect their patients. Consent must be obtained from patients for return of results, and physicians may want to use the various informational tools that are available to help their patients through the process of deciding which results to receive. Given the complexity of genomic results, including variable penetrance and possible preventive interventions, the research study should support physicians in understanding 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, using a communication process tailored to the needs of the individual patient. Engaging genetic counselors in helping patients understand the implications of genomic findings can be helpful because of their scientific understanding of genetic disorders, experience in dealing with patients, and training in counseling skills.

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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 those who agree to participate, drawing a blood sample for the genomic testing, returning the results to your participating patients, and being a member of the team that will assess the 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 unclear (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 patients, explain the study to them, understand and interpret the genetic results for them, and recommend possible follow-up care, as well as whether compensation will be provided for the physician's time and how his or her contribution will be acknowledged.

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

See also:

Web-Only
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In What Laboratory or Laboratories Will the Study Conduct Its Genomic Testing?

Because the results of the study's genomic testing may inform the internist and enrolled patients of potential clinical concerns, it is important that the internist confirm with the research team where the genomic sequences will be generated and the data analyzed. 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 Laboratory Improvement Amendments of 1988 (CLIA) (2), which require 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. Because the explicit purpose of the study in this case is to return genomic information and examine its effect on medical care, the internist will want to be sure that the testing is

Key Summary 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 identify a large number of variants with clinical or personal value to 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 are available 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 support physicians in understanding the results and their implications for patients.

Physicians should be prepared to communicate results in a manner that facilitates patient 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 because they have a scientific understanding of genetic disorders, are experienced in dealing with patients, and are trained in counseling skills.

in fact being done, or the results confirmed, in a CLIA-certified laboratory.

WHAT GENOMIC TEST RESULTS AND ASSOCIATED INFORMATION WILL THE STUDY PROVIDE?

Genomic screening can identify many variants of potential medical relevance. These variants differ in the seriousness of the resulting condition and degree of disease risk; age of onset; availability, cost, burden, and timing of preventive or therapeutic interventions; and opportunity for reversal. Given the need to balance the costs associated with returning findings with the value of the information to clinicians and patients, various 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 and urged 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). In 2018, a report from the National Academies of Sciences, Engineering, and Medicine on return of research results suggested that 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 reason for offering to return results is when they are "clinically actionable"—that is, results that may guide decisions about 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 genes (later revised to 59) associated with potentially life-threatening conditions be available for return as secondary findings in clinical genomic testing, regardless of the original reasons for ordering testing (6). Examples of clinically actionable variants (and preventive interventions) include mutations on the *BRCA1* gene associated with hereditary breast or ovarian cancer (breast cancer screening, mastectomy, and oophorectomy), the *MLH1* gene associated with hereditary nonpolyposis colon cancer (colonoscopy and prophylactic surgery), and the *KCNQ1* gene associated with long QT syndrome (β-blocker use and avoidance of QT-prolonging medication). Pharmacogenomic information can also help identify persons who are at risk for toxicity or reduced therapeutic response when given standard doses of particular medications. However, considerable diversity remains in views about which variants should be returned and under what conditions (7).

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

Although considerable concern has been expressed about adverse psychological effects from receipt of results that have serious health implications or uncertain significance, most studies to date have not reported more than transient distress related to testing. On average, neither long-term anxiety nor depression has been found to increase after testing, although individual variability may be considerable (8). However, these data tend to come from participants who sought genetic testing, received a single result, and were afforded pretest and posttest genetic counseling. Whether adverse responses are more likely in other situations is unclear (9). Risks associated with misunderstanding test results and their implications can include inappropriate action (for example, prophylactic surgery) or inaction (for example, not getting proper screening). Social consequences—such as stigmatization; the economic impact of anticipated changes on

earning potential; and adverse effects on relationships with others, including family members–may also occur (5).

Because returning genomic results may have both clinical and personal utility to participants, 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 are highly interested in genetic results, although that interest varies across specific results (10). It is therefore important to understand "what participants 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). 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 return of results; and issues of privacy and confidentiality, data use and security, and relevance to family members (11). Ascertaining participant preferences for return of results can be facilitated by grouping categories of results into "bins" (12)–for example, medically actionable findings, nonactionable findings that may have implications for life planning, findings with reproductive implications, and pharmacogenetic findings. 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 earlier. Participating physicians will need to consider that allowing patients to decline return of results could mean that potentially life-saving information will not be given 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, participants are informed at the outset of the study that results may be available and that, if the results are relevant, participants will be reapproached to determine whether they would like to receive the results. 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; this may allow a more focused discussion and decision process. It also better enables 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 in the development of a consent process; for example, the toolkit developed by the Multi-Regional Clinical Trials Center contains guidance for informed consent documents, checklists and model language, and 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 presented in laboratory reports that identify the variants 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 for the variant 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 "variant of uncertain significance" (VUS) 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 a VUS when its effect on gene function is not known and data are insufficient to confirm that it is associated with disease risk or is benign (16). Clinicians are generally advised not to use a VUS for clinical decision making. Many genomic screening studies do not routinely report VUSs. Also, variant interpretation may change over time as new information becomes available. Many genetic testing laboratories routinely send an amended report to the ordering physician when a variant is reclassified in a way that would change clinical management (16). The internist in our example should inquire whether this study will reclassify variants and issue revised reports over time.

If evidence suggests that the variant is not associated with a disease condition, that 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 result does not eliminate the possibility of increased genetic risk.

Once the results are in hand, the physician will need to assess the clinical implications and possible clinical actions. This task is complicated by the variable effects of genetic mutations and by incomplete penetrance that depends on age and sex. A growing number of resources and decision support tools are being developed to assist in understanding results, such as Online Mendelian Inheritance in Man (17), ClinVar (18), GeneReviews (19), and the National Comprehensive Cancer Network guidelines (20). Such publications as the "Guide to Interpreting Genomic Reports: A Genomics Toolkit" (16), developed by a consortium funded by the National Institutes of Health, 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, the internist in our case must have access to a geneticist or 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 them in a manner that facilitates patient 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. Educational materials can often help 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). 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). Thus, the internist in our case may play an important role 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, permit them to communicate knowledgeably and effectively with patients. Although the number of genetic counselors is inadequate to serve the increasing number of patients having genomic testing, many studies have shown that education and counseling can be provided effectively via video or telephone and that using genetic counselors to supplement online resources can increase the efficiency of the counseling process (5). If the study does not provide counselors, the National Society of Genetic Counselors has patient and provider resources on its Web site, including a searchable tool to find a genetic counselor near you (22).

Anticipating Greater Clinical Use of Genomic Testing

Most genetic testing of adults, even when sequencing technologies are used, focuses on single genes or a panel of genes rather than the entire exome or genome. Moreover, with rare exceptions, genomic screening of healthy populations is limited to research settings. However, the principles outlined in this article 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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