COMMENTARY | Genetics inMedicine

Genomic screening of the general adult population: key concepts for assessing net benefit with systematic evidence reviews

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Advances in genomic technology allow us to seek information about hereditary conditions before individuals develop symptoms.[1] This raises the possibility of screening the general population for medically actionable variants that predispose to life-threatening, but preventable, diseases. However, critical questions remain regarding how to systematically assess the harms and benefits of such screening in the general adult population.

There is a general consensus that medically actionable genetic information, discovered in a clinical context, should be returned to individuals, although there is less agreement regarding which genetic conditions are "actionable," optimal mechanisms of return, and the practicalities of implementation.[2,3] In seminal recommendations, the American College of Medical Genetics and Genomics endorsed 56 medically actionable genes that clinical laboratories should generally analyze and report in the course of genome-scale sequencing.[4,5] In the research realm, members of two National Human Genome Research Institute consortia argued that researchers should offer participants context-appropriate medically actionable findings when discovered purposefully or by chance.[3]

In contrast to discovery of actionable variants by chance or via opportunistic screening in the setting of whole-exome or whole-genome sequencing, a fundamentally different question is being explored as part of "GENE-SCREEN," a project of the University of North Carolina's National Human Genome Research Institute–funded Center for Excellence in ELSI Research. This project is investigating the feasibility and ethics of screening the general population for highly medically actionable variants in a selected set of genes through targeted next-generation sequencing. To further inform efforts toward the application of genomic technologies to the general population, we explore some of the obstacles to conducting systematic evidence reviews (SERs) in the public health genomic context, describe a conceptual model to guide SERs, and discuss ways in which important obstacles can be productively surmounted.

For GENE-SCREEN, a committee of 16 individuals with diverse training and a community advisory board reviewed and weighed candidate genes and arrived at a list of 17 genes that, when mutated, confer high risk of 11 potentially detectable and preventable disorders.[2] The selected conditions range from cancer to cardiovascular conditions and include, for example, genes associated with Lynch syndrome—a severe, but preventable, condition conferring a high risk of cancer. Complex cost considerations will ultimately be highly relevant to whether targeted genomic screening should be pursued in the public at large. However, we must first analyze whether screening the general population for mutations in these genes may be beneficial for individuals and society, and we must discover areas where evidence is lacking and research must be performed before general implementation.

SYSTEMATIC EVIDENCE REVIEWS

SERs are commonly used to inform the assessment of net benefit: the value of the benefit minus harm of a particular intervention or preventive service, as determined from evidence gathered through a literature review.[6] There are few such reviews of genomic screening to evaluate outcomes, benefits, and harms, and those that exist typically focus on evidence drawn from high-risk populations.[7]

The lack of evidence specific to a pre-symptomatic population creates a "Catch-22" because, although healthy individuals are not generally screened without evidence of net benefit, that evidence will not be developed unless testing in research environments or postmarket studies occurs (e.g., from controlled trials or coverage with evidence development). Until evidentiary gaps, due to either lack of studies or insufficient findings, can be filled, it is difficult to know how to apply the existing evidence of harms and benefits to the general population. Reviewers can view evidence from the high-risk population or patient population as an upper or lower threshold to estimate

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whether overall evidence tips toward net harm or benefit; alternatively they can utilize decision modeling to supplement the evidence found during a SER. A SER for public health genomic screening will likely highlight significant evidentiary gaps, and the process is important to inform the future research agenda. To guide literature selection for a SER, reviewers must consider the following components of a conceptual model.

Penetrance

Understanding the likelihood that a condition will develop if an individual has a causative genetic mutation is an essential, but challenging, component of SERs.[8] Penetrance is usually estimated by examining individuals ascertained as having the disorder in question. Because of ascertainment bias, it is therefore probable that current estimates of penetrance will decrease when we begin to test the general population and discover individuals with apparent deleterious mutations but no disease. Any decrease in penetrance alters net benefit by reducing the overall amount of disease that can be prevented by screening and by exposing people unnecessarily to the potential harms of identification and intervention. To the extent possible, a SER must find penetrance estimates taken from a general population without family history or view penetrance estimates as a ceiling, not an absolute.

Prevalence

Genetic conditions are rare in the population and, until recently, mutation identification has been laborious, making it difficult to develop precise prevalence estimates. SERs must make assumptions or undertake modeling exercises when prevalence is unknown. More individuals must be screened to find an affected individual if prevalence is low, leading to more individuals subjected to harms of testing without realizing benefits. This consideration also typically necessitates minimizing false-positive tests through exclusion of variants of uncertain significance (VUS).

Variants of uncertain significance

The application of genomics to public health must grapple with the reality of VUS and the fact that, contrary to many other screening contexts, there is usually no "gold standard" by which to adjudicate ambiguous results. For example, in mammography, a suspicious finding is definitively adjudicated by biopsy, and in newborn screening, enzymatic assays can adjudicate results. However, VUS typically have no confirmatory options and, if reported as clinically significant mutations, great harm could result from high rates of false-positive results with subsequent overtreatment. Until ways are developed to effectively adjudicate VUS, it is most appropriate to ignore them in public health screening. Although this approach will limit sensitivity (resulting in false negatives), it has the critical benefit of yielding a high degree of specificity (minimizing false positives).

Pleiotropy

When assessing net benefit of screening, a SER must consider all downstream harms and benefits and take into account the effects of learning not only about the most penetrant or most clinically actionable phenotype but also about the impact of other associated phenotypes. In GENE-SCREEN, to make the task of evaluating various phenotypes associated with individual monogenic disorders manageable, discussion has concentrated on a limited number of the most medically important phenotypes and interventions. For example, in the case of Lynch syndrome we focus on colonoscopy or prophylactic surgery to minimize the risk of colon, endometrial, and ovarian cancer, despite the condition's association with other phenotypes that may have less effective interventions (e.g., those for small bowel, biliary system, renal pelvis, and ureter cancer). Failing to account for pleiotropy might overestimate the net benefits of testing by neglecting the potential harms of revealing information about potential outcomes for which there are less effective interventions.[9]

Multiple interventions

SERs are complicated not only by pleiotropy but also by multiple possible interventions. Although there may be one intervention among several that is most effective for prevention, such as risk-reducing mastectomy (versus enhanced surveillance) to diminish harm from a *BRCA1/2* mutation, SERs must consider evidence of benefits and harms as well as uptake for each possible intervention. Again, data may not exist for individuals without a family history, and presymptomatic adults from the general population may be less likely than those who are affected or who have a family history of the condition to opt for more radical interventions such as a prophylactic mastectomy.[10]

Who benefits

Targeted genomic screening may not benefit all segments of the population equally. Relative benefit will depend on prevalence, uptake of and access to interventions, outcomes, patient characteristics and preferences, and inheritance patterns. Researchers must consider how to weigh conditions that primarily affect one gender, that are concentrated in ancestral groups, or that have greater impact on individuals at younger or older ages. The prospect of amplifying the benefits of a screening program by identifying additional at-risk family members is attractive. However, although benefits exist for family members, harms may also be predominately concentrated in the individual tested. For example, it will be important to closely evaluate the benefits and harms of *BRCA1/2* testing in men, given the low penetrance among males. The differential clinical impact of *BRCA1/2* mutations in males and females could conceivably show a net benefit for testing women and a net harm for testing men. Therefore, although there may be benefits of testing family members, the decision to screen men primarily for the benefit of female family members should not be taken lightly. For all genetic conditions, there remains the task of assessing harms and benefits associated with cascade testing of family members.

CONCLUSION

SERs are an integral step to inform assessment of the potential net benefits of targeted genomic screening in the general population, but they must grapple with a number of complicated

conceptual challenges in order to ensure that application of sequencing technologies in the realm of public health has the greatest possible beneficial net impact.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Evans JP, Berg JS, Olshan AF, Magnuson T, Rimer BK. We screen newborns, don't we?: realizing the promise of public health genomics. *Genet Med* 2013;15:332–334.
2. Berg JS, Amendola LM, Eng C, et al.; Members of the CSER Actionability and Return of Results Working Group. Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium. *Genet Med* 2013;15:860–867.
3. Jarvik GP, Amendola LM, Berg JS, et al.; eMERGE Act-ROR Committee and CERC Committee; CSER Act-ROR Working Group. Return of genomic results to research participants: the floor, the ceiling, and the choices in between. *Am J Hum Genet* 2014;94:818–826.
4. Green RC, Berg JS, Grody WW, et al.; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013;15:565–574.
5. American College of Medical Genetics and Genomics (ACMG). ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results, 1 April 2014. https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf. Accessed 10 June 2014.
6. U.S. Preventive Services Task Force Grade Definitions After May 2007, May 2008. http://www.uspreventiveservicestaskforce.org/uspstf/gradespost.htm. Accessed 10 June 2014.
7. Khoury MJ. Dealing with the evidence dilemma in genomics and personalized medicine. *Clin Pharmacol Ther* 2010;87:635–638.
8. Jonas DE, Wilt TJ, Taylor BC, Wilkins TM, Matchar DB. Chapter 11: challenges in and principles for conducting systematic reviews of genetic tests used as predictive indicators. *J Gen Intern Med* 2012;27(suppl 1):S83–S93.
9. Kocarnik JM, Fullerton SM. Returning pleiotropic results from genetic testing to patients and research participants. *JAMA* 2014;311:795–796.
10. Haroun I, Graham T, Poll A, et al. Reasons for risk-reducing mastectomy versus MRI-screening in a cohort of women at high hereditary risk of breast cancer. *Breast* 2011;20:254–258.