HHS Public Access

Author manuscript

Genet Med. Author manuscript; available in PMC 2022 June 22.

Published in final edited form as:

Genet Med. 2021 June ; 23(6): 996–998. doi:10.1038/s41436-021-01141-w.

From genes to public health: are we ready for DNA-based population screening?

Muin J. Khoury[1,✉],

W. David Dotson[1]

[1]Office of Genomics and Precision Public Health, Office of Science, Centers for Disease Control and Prevention, Atlanta, GA, USA.

The opinions expressed in the paper are those of the authors and do not necessarily reflect those of the Centers for Disease Control and Prevention.

Recognizing the emerging role of genomics as a tool for population screening, the American College of Medical Genetics and Genomics (ACMG) has generated two companion guidance documents on DNA-based screening of healthy individuals that appear in the present issue of *Genetics in Medicine*.[1,2] In this commentary, we offer a brief public health perspective on these documents in the context of recent work from the Centers for Disease Control and Prevention (CDC) Office of Genomics and Precision Public Health (OGPPH).

Since the start of the Human Genome Project, there has been a strong belief by scientists and the public that at some point in the future, all of us will have our genomes sequenced in routine health care. In 1999, Dr. Francis Collins articulated a vision for the practice of medicine in 2010 in a hypothetical case of a 23-year-old man who presents to his health-care provider as part of a health checkup and is offered genetic testing for various diseases, to develop a personalized plan for disease prevention and screening.[3] However, the complexities of the science and the cost of technology, the need for large scale clinical and population studies, and a host of ethical, legal, and social issues (ELSI) have prevented this prediction from becoming a reality. Nevertheless, steady progress in science and technology, the conduct of clinical and population studies around clinical validity and utility of genetic information, as well as numerous investigations around ELSI, have helped us move closer to this vision. So much so that the new National Human Genome Research Institute (NHGRI) 2020 strategic vision for improving health at the forefront of genomics includes a bold prediction for 2030: “The regular use of genomic information will have transitioned from boutique to mainstream in all clinical settings, making genomic testing as routine as complete blood counts.”[4]

✉**Correspondence** and requests for materials should be addressed to MJ.K. mkhoury@cdc.gov.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

In the United States, the vision presented above has begun to be realized in multiple health systems and population studies carrying out large scale population sequencing in biobanks and learning health systems research settings, such as Geisinger Health System and the Nevada Genome Project.[5] Nevertheless, in 2020, almost all the implemented applications in genomics in routine clinical care occur in diagnostic settings, most notably in the diagnosis of rare genetic diseases, noninvasive prenatal testing, and cancer genomics to guide cancer therapy. In addition, there are limited data on the implementation of testing and its impact on public health.[6]

GENOMICS AND POPULATION SCREENING: "WE SCREEN NEWBORNS, DON'T WE?"

The use of genomics as a population screening tool long predates the Human Genome Project. Newborn screening is considered as one of the ten great public health achievements of the twentieth century.[7] For more than 60 years, newborn screening has been a component of public health programs and has led to major improvements in outcomes for infants with various genetic, metabolic, and other conditions. In the United States, newborn screening identifies >13,000 newborns annually who will require lifelong specialized health care.[8]

Recognizing the emerging role of genomics as a screening tool across the lifespan, in 2013 Evans et al. called for scientific investigation of the application of genomics in adults in a similar way to newborn screening.[9] The authors urged that a partnership be developed between the genomics and public health communities to better identify individuals who have genetic variants with a high risk of preventable diseases.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) TIER 1 GENOMIC APPLICATIONS

In 2014, CDC developed a relatively simple horizon-scanning method based on a three-tier classification system:

- "Tier 1 […] genomic applications have a base of synthesized evidence that supports implementation in practice.
- Tier 2 […] genomic applications have synthesized evidence that is insufficient to support their implementation in routine practice. Nevertheless, the evidence may be useful for informing selective use strategies […]
- Tier 3 […] applications either (i) have synthesized evidence that supports recommendations against […] use, or (ii) no relevant synthesized evidence is available."[10]

For the past few years, CDC has worked with health-care organizations and public health programs to implement evidence-based recommendations for three primary tier 1 applications involving screening for hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS), and familial hypercholesterolemia (FH). This work has included public and provider education, special programs that address disparities in access to testing and

services, conducting public health surveillance, and policy development.[11] It is important to note that the CDC tier 1 designation is associated with the clinical scenario for testing, not the underlying condition. For example, we are not aware of any current recommendations, or synthesized evidence, to support population screening for *BRCA1* and *BRCA2* pathogenic variants, but there are evidence-based recommendations for screening based on family history and ethnicity.[11] The former application of screening for *BRCA1* and *BRCA2* pathogenic variants could thus be considered tier 3, and the latter application tier 1.

AN EVOLVING RATIONALE FOR DNA-BASED ADULT SCREENING

Increasingly, accepted evidence-based approaches using family history-based screening do not identify most individuals with genetic conditions associated with the three primary CDC tier 1 applications. Several studies have shown that a minority of adults with pathogenic *BRCA1/2* variants are aware that they carry these variants.[5] This may be due to limitations to the uptake of family history and the sensitivity of the family history-based approach. The evidence of failure to identify at-risk individuals is occurring in the context of rapidly declining costs of DNA testing, and improved ability for interpreting pathogenicity of DNA.[5]

It is estimated that about 1% of the population carries a pathogenic DNA variant associated with familial hypercholesterolemia *[LDLR, APOB, PCSK9),* HBOC *(BRCA1, BRCA2),* or LS (*MLH1*, *MSH2, MSH6, PMS2).*[5] DNA-based population screening for these genes can potentially offer short-term benefit for the estimated 3 million individuals in the United States with one of these risks, and longer-term benefit to more people as the number of genes proposed for population screening increases. It is important to note that population screening is distinct from diagnostic testing. Population screening should be evidence-based and adhere to the screening criteria established by Wilson and Jungner several decades ago.[5]

In 2018, the Genomics and Population Health Action Collaborative (GPHAC) of the Roundtable on Genomics and Precision Health of the National Academies of Sciences, Engineering, and Medicine evaluated the potential for DNA-based screening programs in healthy adults. This group developed a roadmap for implementation that should be considered when developing a population-based sequencing program.[12] The group also identified important issues to address such as feasibility of screening, potential benefits and harms, outcomes, costs, and ultimately, clinical utility.

ACMG POINTS TO CONSIDER GUIDANCE DOCUMENTS ON ADULT DNA-BASED SCREENING

The first ACMG points to consider (PTC) document offers guidance for programs and sponsoring organizations that are considering DNA-based health screening,[1] and the second offers guidance to individuals and health-care providers around DNA-based screening.[2] Taken together, the two documents mark an important milestone on the road to public health genomics. They also appropriately reflect the complexities inherent in applying genomic information to healthy populations.

The first document has seven points to help guide programs and sponsoring organizations. The authors review the evolving evidence around DNA-based screening in relation to the well-known Wilson and Jungner criteria[13] for population screening. The document concludes that DNA-based screening efforts have the potential to improve population health, but only if risk identification is effectively combined with evidence-based risk-reducing clinical care. The document embraces the list of genes associated with the CDC tier 1 genomic applications as a core list for consideration in the context of population screening. The conditions involved in the three primary tier 1 genomic applications are specifically associated with risk for breast, ovarian, colon, and endometrial cancers; coronary artery disease; and stroke and are therefore consistent with Wilson and Jungner's guidance to focus health screening on "important health problems." The seven points to consider are detailed and clearly articulated throughout. The authors are to be commended in attempting to deal with the challenging, shifting terrain of increasing use of DNA-based health screening, in programs and organizations, even in the absence of adequate evidence. We fully agree with the statement that "the health service delivery options for DNA-based health screening are currently in flux.... Much of the health services and economic research needed to address the DNA-based screening issues are yet to be done."

The second guidance document is addressed to individuals and health-care providers. It acknowledges at the outset that while the clinical utility of genome sequencing in apparently healthy people has not been established, accessibility to sequencing has increased, including use by the public without any specific clinical indication. The document explores opportunities and challenges presented by the changing models for delivery of genetic testing services. These include (1) a traditional genetic health-care model of services between genetics health-care providers and a patient's referring provider, (2) a nontraditional genetic health-care model where genetic services are integrated within primary care and other specialties, and (3) a consumer-directed genetic health-care model in which consumers initiate the process on their own without involvement of health-care providers. The document offers a framework for the delivery of DNA testing according to the well-known preanalytical, analytical, and postanalytical phases of the testing process. It considers opportunities and challenges for each step of the process and for each health-care model, and strategies to address them.

One of the most useful aspects of the second ACMG guidance document are the detailed steps identified in the pre- and postanalytical phases, which can allow exploration of important components (e.g., preanalytical education step, informed consent, and others). The detailed descriptions in the document allow comparison between different delivery models. This framework provides a helpful analytic tool to evaluate the strengths and weaknesses of each delivery model, and a careful summary of what we know about the delivery models in the three phases, and their strengths and weaknesses. Nevertheless, by acknowledging that the traditional delivery model is being replaced by the nontraditional, such as consumer genetic testing, the document appears to acknowledge the inexorable march toward DNA screening for healthy populations even in the absence of data on clinical utility, economic considerations, and adequate dealing with ethical, legal, and social issues.

DNA-BASED POPULATION SCREENING: WHAT'S NEXT?

The two ACMG documents taken together reflect a new approach by marrying the importance of an evidence-based approach of the first document invoking principles of population screening with the importance of ensuring the integrity, quality, and outcomes of the testing process in the context of changing models of implementation. But the striking differences in the guidance document's presentation and recommendations for individuals and providers versus programs and organizations may be inadvertently confusing to organizations, providers, and individuals, as it may be misinterpreted as DNA-based population screening can proceed without evidence, since it seems to be the only way such evidence can be gathered.

As the first ACMG document clearly shows, there are key knowledge gaps in fulfilling criteria for population screening. One important gap is the incomplete understanding of the "natural history of the condition." Natural history is concerned with the course of disease in the absence of treatment, and it involves both penetrance, the proportion of individuals with a given genomic risk who will show evidence of the associated clinical problems, and expressivity, the range of clinical manifestations associated with a specific genomic risk. While we have a detailed understanding of many genetic conditions in patients identified by diagnostic testing, natural history data are limited for persons identified via DNA-based screening. If DNA-based screening is to improve the public's health, it must be combined with evidence-based care that reduces the burden of disease (e.g., screening, pharmacologic prevention). Management guidelines will need regular reanalysis of DNA variants informed by the most updated curated databases, regular clinical evaluation in screened individuals, the availability of updated clinical decision support tools and linkages with electronic health records, as well as regular assessment of the effectiveness, benefits, and potential harms of testing and prevention strategies. The two documents focus on DNA-based screening and population health related to a limited number of common and well-studied genetic disorders. Other areas where the evidence is more limited (tier 2 or tier 3) include pharmacogenomics, polygenic risk scores (PRS), and additional monogenic conditions.

Ongoing research is needed to evaluate genotype–phenotype correlations in longitudinal studies and biobanks, and clinical utility studies to evaluate the effectiveness of risk-reducing interventions in screened persons with pathogenic variants in associated genes. We have previously proposed a collaborative implementation research agenda embedded in learning health systems[14] to create an adequate evidence base to support DNA-based screening to improve population health. The translational research framework outlines collaboration among multiple health systems with available genome sequencing data and clinical outcomes. The framework is based on evaluating the impact of genetic information on improving health outcomes through research that incorporates levels of evidence for each intended use. Both observational studies and randomized controlled trials may be required to adequately evaluate health benefits, harms, and costs based on returning or not returning the results of gene variants to patients and providers. The proposed approach encourages learning health systems to collect clinical utility evidence in a research environment and develop the capacity for integration of sequencing with other clinical services.[14]

Important implementation questions related to DNA-based population health screening need to be answered.[15] These include, among others: How should screening be designed to offer inclusive benefits for the whole population? What are the appropriate population characteristics for screening? (e.g., age, gender). Who should pay for DNA-based screening and clinical follow-up? How often should data be reanalyzed? What are the clinical workforce needs related to delivering DNA-based results and clinical follow-up at population scale?[15]

Given the relatively low frequency of individuals with genetic risk in the population, pilot studies will require large collaboration to begin to address some of these evidence gaps. Without large pilot studies, opportunities to evaluate evidence of clinical utility and economic feasibility will be delayed. There are no shortcuts on the long road to evidence-based genomic medicine. The same can be said about any population screening program. It is sobering to note that the now well-established population screening for colorectal cancer took several decades to lead to an evidence-based recommendation.[11] DNA-based screening is a relatively new approach for identifying disease risks, and it has the potential to become a population screening program in the years ahead. While we may not be ready for population-based DNA screening, the ACMG guidance documents represent a leap forward in acknowledging the reality on the ground that such screening may already be happening, with or without evidence of clinical utility. The two documents represent a valiant effort in providing guidance and points to consider to health-care organizations, providers, and individuals considering DNA-based screening but should not be construed to imply that we are ready for population-based screening. These efforts should be conducted in the context of research enterprises and learning health systems, which have already started in multiple locations around the country. A collaborative approach will provide a faster approach to answer important outstanding questions of utility and implementation. We hope that collaborative studies including cohort studies and clinical trials can be adequately resourced and vigorously pursued.

Finally, more efforts are needed to engage public health systems, professional societies, and health-care organizations in the dialogue around DNA-based population screening. The two ACMG documents provide a great starting point for awareness and integration of this rapidly changing practice landscape.

REFERENCES

1. Murray MF et al. DNA-based screening and population health: a points to consider statement for programs and sponsoring organizations from the American College of Medical Genetics and Genomics (ACMG). Genet. Med 10.1038/S41436-020-01082-w (2021).
2. Bean LJH et al. DNA-based screening and personal health: a points to consider document for individuals and healthcare providers from the American College of Medical Genetics and Genomics (ACMG). Genet. Med 10.1038/s41436-020-01083-9 (2021).
3. Collins FS Shattuck lecture: medical and societal consequences of the Fluman Genome Project. N. Engl. J. Med 341, 28–37 (1999). [PubMed: 10387940]
4. Green ED et al. Strategic vision for improving human health at the forefront of genomics. Nature. 586, 683–692 (2020). [PubMed: 33116284]
5. Murray MF & Giovanni MA Bringing monogenic disease screening to the clinic. Nat. Med 26, 1172–1174 (2020). [PubMed: 32733075]

6. Phillips KA, Douglas MP & Marshall DA Expanding use of clinical genome sequencing and the need for more data on implementation. JAMA. 324, 2029–2030 (2020). [PubMed: 33104159]

7. Centers for Disease Control and Prevention. Ten great public health achievements. United States: 2001–2010. MMWR Morb. Mortal. Wkly Rep 60, 619–623 (2011). [PubMed: 21597455]

8. Centers for Disease Control and Prevention Public Health Grand Rounds. Newborn screening and improved outcomes. MMWR Morb. Mortal. Wkly Rep 61, 390–393 (2012). [PubMed: 22647744]

9. Evans JP et al. We screen newborns, don't we? Realizing the promise of public health genomics. Genet. Med 15, 332–334 (2013). [PubMed: 23470837]

10. Dotson WD et al. Prioritizing genomic applications for action by level of evidence: a horizon-scanning method. Clin. Pharmacol. Ther 95, 394–402 (2014). [PubMed: 24398597]

11. Khoury MJ et al. From public health genomics to precision public health: a twenty-year journey. Genet. Med 20, 574–582 (2018). [PubMed: 29240076]

12. Murray JF, Evans JM, Angrist M & Genomics and Population Health Action Collaborative. A proposed approach for implementing genomics-based screening programs for healthy adults. National Academy of Medicine, Round Table on Genomics and Precision Health, https://nam.edu/a-proposed-approach-for-implementing-genomics-based-screening-programs-for-healthy-adults/ (2018).

13. Wilson JM & Jungner YG Principles and practice of mass screening for disease. Bol. Oficina Sanit. Panam 65, 281–393 (1968). [PubMed: 4234760]

14. Khoury MJ et al. A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health. PLoS Med. 15, el 002631 (2018).

15. Murray MF, Evans JS & Khoury MJ DNA-based population screening: potential suitability and important knowledge gaps. JAMA. 323, 307–308 (2019).