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Population Screening in Health Systems

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Abstract

Applications of genomics to population screening are expanding in the United States and internationally. Many of these programs are being implemented in the context of healthcare systems, mostly in a clinical research setting, but there are some emerging examples of clinical models. This review examines these genomic population screening programs to identify common features and differences in screened conditions, genomic technology employed, approach to results disclosure, health outcomes, financial models, and sustainability. The diversity of approaches provides opportunities to learn and better understand the optimal approach to implementation based on the contextual setting.

1. INTRODUCTION

If the nineteenth century was the Industrial Age and the twentieth the Atomic Age, the twenty-first may be remembered as the Age of Genomics and Precision Medicine. While this assertion may seem presumptuous given that we are only a bit over two decades into the century, the dramatic breakthroughs in genomics, informatics, and other enabling technologies—culminating in President Obama's call, in his 2015 State of the Union address, for investment in a large-scale precision medicine initiative, the *All of Us* Research Program (13)—would seem to make it plausible.

A prior review that focused on the implementation of genomic medicine programs (53) noted the potential for growth in several areas, including diagnostic testing, somatic tumor analysis, pharmacogenomics, and population screening using genomic sequence. This observation has been borne out over the intervening three years, with evidence of expansion in all of the noted areas, including population screening. The application of genomics to population screening is expanding in the United States and internationally; therefore, focusing this review of population screening on the emerging programs is timely, as it provides an opportunity to examine how these programs are being implemented, the barriers being experienced, their associated solutions, and exploration of the remaining questions to be answered before population screening can be broadly implemented. Before exploring the population screening programs, it is important to provide some background in three areas: population screening in general, population screening using genomics, and health systems.

1.1. Population Screening

Public Health England defines population screening as "the process of identifying healthy people who may have an increased chance of a disease or condition" (41). Screening provides information to the patient and clinician that can inform subsequent tests, treatments, or other interventions for which evidence exists of improved health outcomes. Screening can involve ascertainment of clinical characteristics (e.g., weight and blood pressure), laboratory tests (e.g., glucose and lipids), imaging [e.g., mammography and spiral computed tomography (CT) scans], or other interventions (e.g., colonoscopy). Effective screening requires robust evidence of improved health outcomes for the defined population, at an acceptable societal cost. Some screening, such as blood pressure determination, is applied to all individuals, while other types are restricted to subsets of the population based on personal characteristics such as sex and gender (mammography and prostate-specific antigen), age (colonoscopy), or exposure (spiral CT scans for current or former smokers). Recommendations for population screening are usually adjudicated through organizations specifically tasked for this purpose. The US Preventive Services Task Force is one such organization, and its recommendations are used to prioritize implementation of and reimbursement for population screening programs in the United States.

1.2. Population Screening Using Genomics

Given the relatively recent appearance of genomics, at least when narrowly defined as genomic sequencing, one might conclude that population screening using genomics is also a recent phenomenon.[1] However, if the definition of genomics is appropriately expanded to include family history, it is clear that this information has been used for decades as a way of "identifying healthy

[1]For the purposes of this review, genomic sequencing means data generated by massively parallel sequencing (sometimes referred to as next-generation sequencing). This includes genome sequencing (sequencing

people who may have an increased chance of a disease or condition." As far back as 1997, the US Centers for Disease Control and Prevention (CDC) established the Office of Public Health Genomics and charged it with "identifying, evaluating, and implementing evidence-based genomics practices to prevent and control the country's leading chronic, infectious, environmental, and occupational diseases" (9). In 2019, this office was renamed the Office of Genomics and Precision Public Health to reflect increasing emphasis on nongenomic precision health applications.

Emphasis on the use of family history to identify individuals who would benefit from enhanced surveillance or other interventions is supported by national programs, such as My Family Health Portrait through the US Office of the Surgeon General, and the designation of November as Family History Month, to encourage families gathered to celebrate Thanksgiving in the United States to share family health history. These efforts are not limited to the United States. For example, in the Netherlands a national program using family history coupled with genetic testing was used to identify individuals at risk for early cardiovascular events due to familial hypercholesterolemia (50).

Family history, while a valuable screening tool, has several limitations that degrade its sensitivity in practice. These include lack of sharing of information between family members; the small family size in many developed countries, which affects the likelihood of expression of genetic risk factors; challenges in collecting detailed family history information in the setting of a busy clinic; and the inability to easily access and use the information during clinical encounters, since it is represented mostly as text or images that do not support retrieval and analysis that can be facilitated by information systems through computerized decision support. These deficiencies have led to interest in the use of genomic sequence information for population screening, an approach discussed in detail below. However, this should not be interpreted to mean that family history does not have value as a tool for genomic population screening. In addition to its utility for risk stratification, family history information captures shared environmental exposures and genetic predispositions that have value in stratifying risk irrespective of the presence or absence of a high-impact sequence variant.

The scope of this review is limited to the use of genomic sequence for screening purposes.

1.3. Health Systems

One might reasonably ask why a section devoted to the definition of health systems is even necessary. For most of the world, this section would be less important, given that healthcare is organized and paid for through national health systems. These systems develop population screening programs through standardized national processes that consider evidence of improved outcomes and cost of screening. This approach allows for the prioritization of programs with the highest value (as defined by a relationship between outcomes and cost to achieve the outcomes). These systems are also well suited to initiate pilot programs to generate the data needed to determine whether a new screening program should be implemented. This is not to say that countries do not have regional differences within the national program or that private healthcare options do not exist, but these regional and private systems generally do not initiate or manage country-wide population screening programs.

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of all coding and noncoding DNA), exome sequencing (sequencing of coding regions and associated known regulatory elements—approximately 1.5% of the genome), and panels of selected genes relevant to a defined indication or context. These different approaches will be assumed to provide equivalent information for population screening. The specific type of sequencing used by a described program is included if known.

The situation in the United States is less straightforward. Lee Tunstall, in an article optimistically titled "Making Sense of the U.S. Health Care System: A Primer" (48), states,

> The U.S. health care system is not a universally accessible system—it is a publicly and privately-funded patchwork of fragmented systems and programs. Insured Americans are covered by both public and private health insurance, with a majority covered by private insurance plans through their employers. Government-funded programs, such as Medicaid and Medicare, provide health care coverage to some vulnerable population groups. The government also publicly funds coverage through Indian Health Services and the military.

This system leads to several consequences, as outlined by De Lew et al. (16):

- The United States spends more on health care services than does any other nation. (p. 151)
- Despite the highest health expenditures in the world, the United States does not perform particularly well in terms of gross health outcome measures. (p. 157)
- The United States primarily relies on employers to voluntarily provide health insurance coverage to their employees and dependents; government programs are confined to the elderly, the disabled, and some of the poor. (p. 151)
- These private and public health insurance programs all differ with respect to benefits covered, sources of financing, and payments to medical care providers. There is little coordination between private and public programs. (p. 151)
- Health services are provided by a loosely structured delivery system organized at the local level. (p. 151)
- Municipal and county public health departments provide limited primary care services through public health clinics. (p. 151)
- There is no health planning at the Federal level, and State planning efforts vary from none to stringent review of hospital and nursing home construction projects. (p. 151)

The result is that only one population screening program has a national implementation: newborn screening. The US Department of Health and Human Services has a national planning process for newborn screening; the screening programs themselves are managed at the state and territory level, and although they vary, they do incorporate a recommended uniform screening panel. Newborn screening is incorporating genomic sequence information as part of the process to guide diagnosis and treatment. Some discussions about the role of exome or genome sequencing as part of newborn screening have begun, but implementation is likely years away. Therefore, newborn screening is not considered as part of this review.

2. METHODS

The focus of this narrative review is programs that are using exome or genome sequencing for population screening in a clinical or clinical research setting based in a healthcare system. Research done in clinical care settings is included, as there are almost no implemented clinical programs that do not have an associated research component. To be included, a program must be actively returning results to participants or have a well-described plan for returning results that will be implemented in the near future. The review excludes programs that focus only on pharmacogenomics; programs that focus only on carrier screening; programs that screen for single genes; and programs that return only polygenic risk scores for risk stratification, without other use of sequence information. It also excludes research studies that are conducted within a healthcare system, are focused on a group that is not representative or inclusive of the broader system, are not open to the participation of any interested patient in the system, or do not have plans to generalize throughout the system.

Three strategies were used to identify relevant materials: (*a*) a search of PubMed, (*b*) a review of programs from the International HundredK+ Cohorts Consortium (IHCC) (described below), and (*c*) the author's personal knowledge of programs. Details of each strategy are described briefly below.

2.1. PubMed

An initial targeted search was performed using the strings "genomic" AND "population screening," "precision medicine" AND "population screening," and "precision health" AND "population screening." Filters limited results to human and English literature. The search dates encompassed literature from 2015 to present, based on the first genomic population screening program going live in 2015. Titles from each search result were reviewed, and an initial list of relevant articles was created. The abstracts of these articles were then reviewed to identify the most relevant ones for full-text review. Final inclusion/exclusion decisions were made after the text review. A second search was performed using the similar-articles function for all selected articles. A third approach using Medical Subject Headings (MeSH) terms was not used due to issues discussed in Section 4.5. The reference lists for all included articles were also reviewed to identify other relevant articles missed by the search strategy.

2.2. The International HundredK+ Cohorts Consortium

The IHCC (32) has assembled a group of large population cohorts that have agreed to share data to address questions that require population sizes beyond that of any single cohort. It was convened by the National Institutes of Health and the Wellcome Trust in collaboration with the Global Alliance for Genomics and Health and the Global Genomic Medicine Collaborative. As of 2020, it included 103 cohorts from 43 countries with nearly 50 million participants. A subset of these cohorts met the inclusion criteria for this review. Information was obtained from the IHCC coordinating center, the IHCC website (24), program publications, and the websites of individual programs. Additional programs are represented in the IHCC, although analysis of these programs is limited because the publicly available database does not specify whether a given cohort project includes massively parallel sequencing in the genomic analysis, nor does it indicate which cohorts are returning results to patients or participants. To ensure completeness, the links provided by each program were used to visit the project webpage to see whether additional information allowed inclusion of the project. Absent information supporting return of results, cohorts were excluded from further analysis unless identified by another strategy.

2.3. Purposive Sampling

The author has been personally involved in a large genomic population screening study, Geisinger's MyCode Community Health Initiative (54), which has led to participation in projects such as the IHCC and invitations to consult with programs that are initiating population screening using genomics. This activity provided additional insights, particularly in the areas of financial support and sustainability, that may not be available in publications or publicly available materials. This knowledge was used to provide insights into these critical areas. Any published articles from these programs were reviewed and their reference lists searched as in the PubMed strategy.

3. RESULTS

The search strategy defined in Section 2.1 identified 119 publications for title and abstract review. The topics of the retrieved articles fell into two general categories: (*a*) population screening

programs that focus on specific conditions implemented across multiple systems and (*b*) population screening programs that use genomic sequence information to screen for multiple conditions within a healthcare system.

3.1. Condition-Specific Population Screening

The search identified some population screening programs that were focused on a condition or group of conditions.

3.1.1. Population screening for hemoglobinopathies. The most frequent conditions undergoing population screening identified in this search were the hemoglobinopathies, a topic that was reviewed in this journal in 2018 (19). These conditions were not considered for this review, based on exclusions such as carrier screening, newborn screening, and use of screening technologies other than genomic sequencing.

3.1.2. Population screening for cancer predisposition. The second most frequent condition was cancer predisposition. The most common cancer predisposition for which population screening is employed is hereditary breast and ovarian cancer (HBOC); the focus of the screening is on the risks associated with pathogenic/likely pathogenic (P/LP) variants in two genes, *BRCA1* and *BRCA2*. This screening was the subject of a review in this journal in 2020 (31) that presented the argument for universal testing. Below, I briefly describe publications from several systems that have reported results for population screening for HBOC.

Strategies have varied across screening programs. Studies prior to 2015 generally reported findings from screening small convenience samples of patients presenting with a personal or family history consistent with HBOC. More recently, some studies (representative examples referenced) have expanded screening to larger higher-risk populations identified using guidelines such as those from the National Comprehensive Cancer Network (5, 17) or those with a personal history of breast and/or ovarian cancer (3, 8, 14, 36, 43, 44). These studies have been performed in a wide variety of settings internationally, including North America, Brazil, North Africa, South Africa, the Middle East, Asia (including large studies in China, India, and Japan), and Europe. When the genomic analysis includes both P/LP single-nucleotide variants and copy-number variants and rearrangements, the rate of positive tests is quite high, ranging from approximately 15% to 25%, with higher frequencies seen in studies focusing on ovarian cancer. These rates are remarkably consistent across the different countries despite each country identifying pathogenic founder variants of relevance to its population.

These findings coupled with other epidemiologic evidence have led to studies of screening of unselected populations for HBOC using genomic sequencing. Most of these studies focused on screening individuals of Ashkenazi Jewish ancestry for the three Ashkenazi Jewish founder variants in *BRCA1* and *BRCA2* (20, 30, 34), while a study in the Bahamas examined an unselected Bahamian population for founder variants seen in the Bahamas (47). These studies all found that the criteria used to identify individuals at high risk for HBOC miss a significant number of individuals with P/LP variants in these selected populations. Despite this, this review did not identify any population screening program for HBOC that had been implemented.

3.2. Genomic Screening Programs for Multiple Conditions

Most population screening programs do not focus on a single condition; rather, they take advantage of massively parallel sequencing strategies, including exome sequencing, genome sequencing, and panels, to interrogate anywhere from nine to several hundred genes in a single assay. These

programs are generally agnostic to health status and thus are described as unselected, although the impact of bias from referral, including self-referral, is discussed below. Screening programs have been established internationally at the levels of countries or regions and in the United States at the state level down to the individual health system. What follows are program descriptions presented in a standard format that allows assessment of program variation to support conclusions about strategies, facilitators, and barriers. An attempt was made to be comprehensive, but limitations in the information available for the search strategy (see Section 4.5) may have led to some programs being inadvertently omitted.

3.2.1. International programs. An overview of international approaches to integration of genomics into healthcare was published in 2019 (45). Projects in some countries are limited to infrastructure development (Finland and Switzerland), while those in other countries, in addition to infrastructure, are developing cohorts around specific conditions such as cancer, rare diseases, and cardiovascular disease [Australia, Netherlands, and the United Kingdom (Genomics England)]. Projects in several countries have developed or are intending to develop population cohorts [Denmark (both Genome Denmark and FarGen in the Faroe Islands), Estonia, France, Japan, Qatar, Saudi Arabia, Turkey, the United Kingdom (the Scottish Genomes Partnership, Welsh Genomics for Precision Medicine Strategy, and Northern Ireland Genomic Medicine Centre), and the United States]. A systematic review published in 2021 (28) identified 86 countries with national genomic projects, of which 41 were noted to be active. Only 15 of these 41 projects (37%) had proposed strategies for the implementation of genomic medicine, although specifics about return of results were not explicitly addressed. The international programs described below are known to include both of these inclusion criteria, but others may have been inadvertently excluded due to lack of available information for these criteria.

3.2.1.1. Estonia: the Estonian Genome Project (40).

- Year established: 2001. Return of results was initiated in 2017.
- Focus: Piloting a genome-first approach to population screening for genetic disease in Estonia.
- Genomic analysis and return of results: Genome sequencing on 3,000 participants and exome sequencing on 2,500 participants. Invitations to receive results were sent by mail, and individuals who responded were scheduled for a disclosure visit with a clinical genetics specialist and other relevant specialists at either Tartu University Hospital or the North Estonia Medical Centre.
- Population and enrollment target: Participants were from the general Estonian population, with additional selection to obtain broad representation across Estonian ancestral groups. There was no selection for medical conditions. Phase 1 enrollment was just over 52,000 individuals, and a second enrollment phase added another 150,000 participants; these 202,000 participants represent approximately 20% of the Estonian population. Cascade testing is offered to at-risk relatives of participants.
- Participant cost and funding: There is no participant cost. Funding was obtained from a variety of sources, including the Estonian Research Council, agencies of the European Union, and the US National Institutes of Health.
- Health system and partners: Tartu University Hospital, the North Estonia Medical Centre, the Broad Institute, the Nestlé Institute of Health Sciences, and the government of Estonia.
- Initial results: Analysis at this point is limited to the original 52,000 participants. An initial study that focused on familial hypercholesterolemia (4) was discussed in a prior review in this

journal (53). This project has subsequently published on the disclosure of P/LP variants in *BRCA1* and *BRCA2* to participants (29). Of the 22 participants who chose to receive results, only 8 (36%) were classified as high risk by the National Comprehensive Cancer Network criteria. The study also presented health outcomes data demonstrating that more than half adhered to recommended enhanced surveillance, and 5 of 16 eligible women (31%) underwent risk-reducing surgery. Relatives of 10 participants elected to pursue cascade testing.

3.2.1.2. Newfoundland, Canada: Sequence Bio's NL Genome Project (37).

- Year established: 2018.
- Focus: "By studying our province's one-of-a-kind DNA and health information, we hope to discover better, safer medicines and improve how we treat and prevent diseases" (37).
- Genomic analysis and return of results: Initial genotyping followed by genome sequencing. The project intends to return medically actionable variants in 59 genes, carrier status (number of genes unspecified), and personal traits (eye color, caffeine metabolism, etc.). The project specifically states that the results returned will be "research-grade" (37) and will not be placed in the participant's medical record. The results will be returned to the participant's physician, and the physician then needs to order clinical tests to confirm those results.
- Population and enrollment target: The targeted enrollment is 10,000 participants. Enrollment takes place through a panel of participating physicians in Newfoundland, and physicians are compensated for costs associated with enrolled patients. Current enrollment is not listed on the project website.
- Participant cost and funding: There is no cost to participants. Funding is provided by Sequence Bio. There is no mention of coverage for clinical testing or subsequent care, so these costs presumably would fall to the patient or healthcare system. Genetic counseling is provided at no charge through Sequence Bio.
- Health system and partners: Sequence Bio, a private, Newfoundland-based biotechnology company. No other partners are listed. Physicians are from multiple clinics, but there is no indication of alignment with the Canadian national health service.
- Initial results: No results are available at this time.

3.2.2. US state-based programs. Two states have implemented genomic population screening programs, with others in development.

3.2.2.1. The Healthy Nevada Project (23).

- Year established: 2016.
- Focus: "The Project aspires to offer genetic testing to any Nevadan interested in learning more about their health and genetic risks while serving as a model for other communities across the country" (23).
- Genomic analysis and return of results: Clinical exome sequencing. Analysis focuses on genetics associated with three CDC Office of Genomics and Precision Public Health tier 1 conditions (10): HBOC, Lynch syndrome, and familial hypercholesterolemia. Return of results began in 2018.
- Population and enrollment target: Enrollment is open to any Nevada resident but is currently focused on northern Nevada. The targeted enrollment is 250,000 participants. The initial enrollment of 10,000 was completed in 2016, and in 2018, the program expanded to include an additional 40,000 participants.

- Participant cost and funding: There is no cost to participants. Funding is provided by the Renown Institute for Health Innovation and a grant from the state of Nevada.
- Health system and partners: Renown Health (participants are not required to be members of the system or to have health records at Renown), with testing provided by Helix. Other partners include the Desert Research Institute and Genome Medical.
- Initial results: The Healthy Nevada Project published its first outcomes study in 2020 (21), analyzing the first results reported between October 2018 and August 2019. The genetic analysis identified 214 unique P/LP variants, which were carried by 358 individuals out of a total population of 26,906 (population prevalence of 1.33%). Electronic health records were available for 273 participants and 20,190 controls. Of the 273 participants, 60 (22%) had evidence of a personal history of a condition relevant to the actionable gene of interest, which was significantly higher than the rate for controls for all three of the CDC tier 1 conditions. The study noted that of the variant carriers, only 25% met current criteria for genetic testing. Fewer than half of the participants who met criteria for genetic testing had received testing.

3.2.2.2. The Alabama Genomic Health Initiative (18).

- Year established: 2017.
- Focus: "The program is aimed at preventing and treating disease, including certain types of cancer, heart problems, and genetic disorders. The program will also provide pharmacogenetic analysis to evaluate how participants may respond to certain medications" (49). The program is evaluating genomic approaches in two cohorts: an undiagnosed rare-disease population and the general unselected population for screening. The latter is the focus of the discussion here.
- Genomic analysis and return of results: For the population cohort, high-density genotyping "to detect rare, damaging variants in highly penetrant, medically actionable genes" (18, p. 780). The variants are derived from the American College of Medical Genetics and Genomics (ACMG) Secondary Findings version 2.0 (SF v2.0) gene list, which included 59 genes (26). These variants and selected pharmacogenomic variants are returned to participants and their providers.
- Population and enrollment target: The population cohort is open to any resident of Alabama. The enrollment target is not available in public materials. As of the publication of initial results, 5,369 participants had enrolled in the population cohort.
- Participant cost and funding: There is no cost to participants. The program is funded by the state of Alabama.
- Health system and partners: The University of Alabama at Birmingham, with laboratory services provided by HudsonAlpha. No other healthcare systems, laboratories, or payers are listed as partners.
- Initial results: The initial publication (18) reported that 81 results were returned to 80 participants from the genotyping, or 1.5% of the population cohort. Of these, 58 (73%) had a personal or family history of a condition deemed relevant to the gene as defined by the study criteria, which the authors noted could represent some ascertainment bias. A follow-up publication (6) pointed out some potential issues with the use of genotyping arrays for variant detection. Of the 131 variants identified on the genotyping platform, 67 (51%) were false positives, as determined by Sanger sequencing. Notably, the rate of false positives in individuals of African American ancestry was significantly higher, highlighting the issues related to the lack of diversity in variant databases.

3.2.2.3. In Our DNA SC (33).

- Year established: 2021.
- Focus: Improving health outcomes by integrating genetic insights into clinical care and research.
- Genomic analysis and return of results: Details are not currently available.
- Population and enrollment target: The program is open initially to patients at the Medical University of South Carolina but will eventually be open to all residents of South Carolina. The target enrollment is 100,000 patients in four years.
- Participant cost and funding: There is no cost to participants. Funding information was not included in the program announcement.
- Health system and partners: The Medical University of South Carolina, with testing provided by Helix.
- Initial results: No results are available at this time (as no patients have yet enrolled).

3.2.4. US healthcare systems. This section describes programs that have been initiated within a healthcare system entity.

3.2.4.1. Mount Sinai Health System BioMe (11).

- Year established: 2007 for the biobank. A return-of-results pilot program started in 2019.
- Focus: Leveraging genomics and big data to elevate medical decision-making and optimizing the customization of healthcare. Another area of emphasis is representation of ancestral diversity, with the goal to establish "a cohort unmatched in ethnic, socio-economic, and medical diversity" (11).
- Genomic analysis and return of results: Exome sequencing with clinical confirmation of putative pathogenic results. The initial focus was on the CDC tier 1 conditions, but in 2019, a fourth condition, hereditary transthyretin amyloidosis, was added, as this condition predominantly affects African-ancestry populations in the United States, which supports the focus of the project. The analysis for hereditary transthyretin amyloidosis was limited to analysis of genotype data for the common pathogenic variant leading to the amino acid substitution V142I in the TTR protein. At present, the return-of-results program is limited to participants who are at least 18 years of age.
- Population and enrollment target: The program is open to any patient in the Mount Sinai Health System. No specific enrollment target has been reported. As of 2021, more than 55,000 participants have enrolled, 65% of whom self-report non-European ancestry.
- Participant cost and funding: There is no cost to participants. Funding is provided by the Andrea and Charles Bronfman Philanthropies and institutional funding to the Charles Bronfman Institute for Personalized Medicine by the Icahn School of Medicine at Mount Sinai. Research exome sequencing is provided by the Regeneron Genetics Center.
- Health system and partners: The Mount Sinai Health System, the Charles Bronfman Institute for Personalized Medicine at the Icahn School of Medicine, the Regeneron Genetics Center, and Sema4.
- Initial results: A pilot program for return of results was initiated in 2019 (1). At the time of this report, 692 participants had updated their consent to include return of results, of which 94 (13.6%) had a research result. After one patient withdrawal, 93 variants underwent clinical confirmation, and 78 were confirmed, of which 34 were the TTR V142I-associated variant. Of the 78 confirmed results, 74 were returned to participants, and 80% of these

individuals were unaware of the genomic variant prior to disclosure. The presence of a disease or phenotype associated with the genomic variant was not ascertained.

3.2.4.2. Geisinger clinical DNA screening program.

- Year established: 2018.
- Focus: Providing clinical exome sequencing in a primary care setting.
- Genomic analysis and return of results: Clinical exome sequencing. The genes analyzed from the sequence include those on the ACMG SF v2.0 list. Test results that include positive findings are reviewed by Geisinger's clinical genomics team and returned to the ordering clinician and to patients through the MyGeisinger patient portal tethered to the patients' electronic health records. Positive results are disclosed to patients by a genetic counselor, at which point patients are given the opportunity to schedule a follow-up appointment. Patients with negative results receive a letter explaining the negative screening results that is uploaded to their electronic health record with the laboratory report.
- Population and enrollment target: Testing is available to any Geisinger patient who is at least 18 years of age and under the care of a clinician in a selected set of primary care and specialty clinics. The pilot has funding for approximately 2,000 patients.
- Participant cost and funding: There is no cost to patients. The testing and interpretation costs are covered by Geisinger Research and the Geisinger Health Plan, supplemented with a philanthropic gift from the Mericle Foundation.
- Health system and partners: Geisinger, Geisinger Research, the Geisinger Health Plan, and the Mericle Foundation.
- Initial results: Analysis of outcomes follows the same process as the MyCode Community Health Initiative. Initial results were presented at the 2020 Annual Meeting of the American Society of Human Genetics (46) and are in preparation for publication. At that time, 870 tests had been completed, with a screen positive rate of approximately 3%, with just under half of these results related to a CDC tier 1 condition. The majority of screen positive results were not previously known to the patient. Just over half of the patients with a result in a CDC tier 1 gene had a personal or family history of disease relevant to the specific gene. For the other genes, more than 80% had no evidence of a personal or family history of the relevant condition within the electronic health record.

3.2.4.3. Northshore University HealthSystem DNA10K (38).

- Year established: 2019.
- Focus: Improving patients' health outcomes at a population level, with genomics as a foundation for informing individualized healthcare. Patients in the program can also opt in to research opportunities.
- Genomic analysis and return of results: Genome sequencing. Results are available for variants in single genes associated with disease risk and pharmacogenomic information. Genomic information is used to determine whether the patient is at higher risk for conditions such as breast and colorectal cancers and heart disease and to inform prescribing decisions. The analysis includes 30 cancer predisposition genes, 30 cardiovascular genes, and 14 pharmacogenes (15).
- Population and enrollment target: The program is available to any NorthShore patient who is at least 18 years of age; 10,000 patients will be eligible to participate. For $50, first-degree relatives of an enrolled patient who are not NorthShore patients themselves can receive cascade testing for a result found in the patient.

- Participant cost and funding: During the initial pilot phase, testing was free to patients. In 2020, the model changed such that patients will be charged $175 for the test. The option exists for insurance to be billed if testing is covered. Patients can also go directly to Color and receive testing for $249.
- Health system and partners: NorthShore University HealthSystem, with testing provided by Color.
- Initial results: From the initiation of the program to January 2020, more than 14,000 patients consented to participate (15). At the time of the initial report's publication, more than 10,000 patients had an order placed for testing, and 9,797 had completed testing. Of the patients who completed testing, 813 (8.3%) had at least one result in an actionable gene, and 116 (1.2%) had a result in a gene associated with one of three CDC tier 1 conditions (HBOC, Lynch syndrome, and familial hypercholesterolemia). Virtually all patients received a pharmacogenomic result. No health or economic outcomes data have been published to date.

3.2.4.4. Penn Medicine preventive genomic screening program (39).

- Year established: 2020.
- Focus: Providing personalized preventive genomic evaluations.
- Genomic analysis and return of results: Exome sequencing and a pharmacogenomic panel. Results include genetic risk for developing conditions such as cancer, cardiovascular disease, and neurologic conditions; carrier status; and pharmacogenomic information. Tests must be ordered by a Penn Medicine medical genetics physician after an in-person or video consultation. Results are returned through an in-person or video meeting with a medical geneticist, genetic counselor, and pharmacist specializing in genetics.
- Population and enrollment target: The population is not specified in publicly available materials. There do not appear to be any restrictions. This screening is being included as part of an executive health program.
- Participant cost and funding: There is a fee for service to patients; the cost is not listed publicly. Discounted rates are available for members of a concierge medical service, Penn Passport.
- Health system and partners: Penn Medicine.
- Initial results: No results are available at this time.

3.2.4.5. University of Vermont Health Network genomic population health program (51).

- Year established: 2020.
- Focus: Performing clinical genomic testing for healthy people.
- Genomic analysis and return of results: The Vermont Genomic DNA Test has two components: health risk genes and carrier genes. The health risk genes test sequences a large panel of genes looking for P/LP variants that increase the risk for different diseases, including cardiovascular disease (77 genes), cancer (61 genes), and other diseases (10 genes). The carrier genes test looks for carrier status in 301 genes. The results are reviewed by a genetics expert and placed in the patient's electronic health record. The patient's primary care provider is in charge of the results disclosure. There is access to genetic counseling, and specialist referral as needed.
- Population and enrollment target: The program is open to any patient who is at least 18 years of age and has a primary care physician from the University of Vermont Health Network who is part of the OneCare Accountable Care Organization. It offers cascade testing for

at-risk family members. Because the testing is purely clinical, there is no specific enrollment target.

- Participant cost and funding: There is no cost to patients for the test or for any genetic counseling provided by University of Vermont Health Network system counselors.
- Health system and partners: The University of Vermont Health Network and OneCare Vermont (a subsidiary of the University of Vermont Health Network).
- Initial results: According to the project website (51), 61 patients had been tested as of April 30, 2020. No other results have been published at this time.

3.2.4.6. Intermountain Healthcare HerediGene (25).

- Year established: 2020.
- Focus: Studying the genes of participants to better predict and prevent serious diseases. This is a research study with the potential for participants to receive medically significant results for clinical care.
- Genomic analysis and return of results: Genome sequencing. Participants can opt in to receive results that the study considers medically actionable. These results are returned through the research study, not through clinical care.
- Population and enrollment target: The program is open to any resident of the United States, regardless of age. It expects to enroll 500,000 participants.
- Participant cost and funding: There is no cost to participants. Funding is from Intermountain Healthcare and the project partners.
- Health system and partners: Intermountain Healthcare, deCODE genetics, and Amgen.
- Initial results: No results are available at this time (results disclosure did not begin until July 2021).

3.2.4.7. NorthShore University HealthSystem and Sema4 genomics program (12).

- Year established: 2021.
- Focus: Using genomic insights to prevent, detect, and manage diseases within a larger personalized medicine program. A strategic partnership will focus on leveraging health intelligence within a clinical care setting.
- Genomic analysis and return of results: Not currently defined.
- Population and enrollment target: The program is available to NorthShore patients. To address disparities in care and underserved populations, enrollment is also being offered to patients at Swedish Hospital, an Illinois safety net hospital located in a federally designated medically underserved area. Genetic testing costs for Swedish Hospital patients are subsidized by the Swedish Hospital Foundation.
- Participant cost and funding: Details about cost are not publicly available, but based on comments about subsidized costs for some patients, there will likely be out-of-pocket costs for patients.
- Health system and partners: NorthShore University HealthSystem and Sema4.
- Initial results: No results are available at this time.

4. DISCUSSION

Genomic population screening programs based in healthcare systems are beginning to increase in number. This is especially the case in the United States, although many international programs are far along in preimplementation and are likely to begin enrolling patients/participants in the

next several years. This review of implemented programs has identified many similarities but also some key differences in the acquisition and disclosure of the information and the approach to financing and sustainability. Outcomes of the programs are beginning to be published, and cost-effectiveness analyses are being undertaken. There may be opportunities to learn about the impact of these programs more quickly if information can be standardized and aggregated through groups like the IHCC. Early efforts at outcome harmonization applied across different programs have illustrated the value of this approach (52).

4.1. Genomic Testing and Interpretation

A variety of methods are being used in the programs described, including exome sequencing, genome sequencing, gene panels, and genotyping panels. Some programs use sequencing coupled with genotyping panels designed to assess pharmacogenomic variants or variants associated with disease carrier status. No preferred method is emerging as yet, although the continued improvements and decreasing cost of massively parallel sequencing will likely drive use of more comprehensive methods.

Variant interpretation seems more consistent between programs, in that most are using variant annotation standards such as those from the ACMG (42). Programs are also limiting disclosure to P/LP variants. This is an important distinction between sequencing done in the setting of screening and a test done for a clinical indication. The latter has a higher prior probability that a variant found in a disease-associated gene is causal, and therefore interpretation and reporting should be more inclusive of variants of uncertain significance, as increased sensitivity is desirable in a diagnostic setting. By contrast, when screening is performed, much more conservative reporting is appropriate, given the lower prior probability of a condition in a given individual. Variants of uncertain significance are much more likely to represent false positives in the setting of screening, leading to inappropriate care recommendations (27).

Lastly, only a few programs have explicitly addressed the question of storage and reanalysis of the genome sequence over time. Germline genomic information is essentially stable over the lifetime of an individual, offering the opportunity to reevaluate the sequence at different points in time or for specific indications (e.g., analysis for carrier status for reproductive decision-making, pharmacogenomic inquiry prior to medication initiation, or diagnostic testing for onset of neurodegenerative disease). There are numerous logistical barriers to address (particularly in the United States, where there is no national healthcare system), but the value proposition for sequencing a population would be enhanced through reuse of the sequence over time.

4.2. Conditions for Population Screening

There is some variability in the types and number of conditions that are evaluated as part of population screening programs. However, virtually all the programs have included analysis of genes associated with three CDC tier 1 conditions: HBOC, Lynch syndrome, and familial hypercholesterolemia. This has been very useful for comparison across different populations. Despite the relatively small numbers reported at present, the results around these three conditions have been consistent, and three conclusions seem evident: (*a*) These three conditions are relatively common hereditary conditions across all populations screened to date; (*b*) current guidelines to identify at-risk individuals relying on personal and family history of disease are insensitive, missing anywhere from 50% to 90% of pathogenic variant carriers; and (*c*) even individuals who meet guidelines for testing are not being uniformly tested, with roughly half of variant carriers not having been offered clinical testing despite meeting testing criteria. These factors lead to lost opportunities for prevention and early intervention that can reduce morbidity and mortality.

Another observation is that many of the projects are using the ACMG SF list [usually v2.0 (26)] as a basis for an expanded set of conditions to be included. This is understandable, given that the genes chosen for this list have been reviewed for evidence of actionability. However, incidental analysis of genes from exome and genome sequencing that are not directly related to the indication for testing should not be equated to population screening. A statement from the ACMG Board of Directors (2, p. 1467) notes that the SF list "was not validated for general population screening" and goes on to state that "the ACMG encourages further ascertainment of genotype–phenotype correlation and research to establish the efficacy of interventions in asymptomatic patients with pathogenic and likely pathogenic variants in known associated genes." The ACMG is currently working on guidance for population screening using genomic approaches. A third version of the ACMG SF list has increased the number of reportable genes from 59 to 73 (35). It will be interesting to see whether population screening programs currently using ACMG SF v.2.0 modify their reporting and reanalyze prior sequences to reflect any updates.

Concern has been raised that use of genomic population screening could identify individuals carrying putative pathogenic variants who will never develop the relevant condition and therefore will have interventions that will not provide benefit. This is a valid consideration in that most of the population prevalence information on these conditions has been derived from studies of families that are more severely affected and thus more likely to come to medical attention. However, early data from programs such as the Geisinger MyCode Community Health Initiative (7), the Healthy Nevada Project (23), and the Estonian Genome Project (4, 29) provide evidence that the prevalence of disease in variant-positive individuals identified through population screening is high enough to mitigate concerns about overtreatment. More importantly, these programs are also demonstrating that these individuals are likely to change health behaviors to incorporate more intensive surveillance, risk-reducing surgery, and medication change to reduce the risk of developing disease or identifying it earlier so that treatment can be more effective. One caveat is that there is some evidence of self-referral for participation of individuals who perceive themselves to be at higher risk. This evidence was quantified in the reports from the Healthy Nevada Project (23), Bio*Me* (1), and the Estonian Genome Project (4, 29). Such self-referral could lead to overestimates of the effectiveness of the programs and is an important area to study as more programs are implemented.

4.3. Funding and Sustainability

There is a high degree of variability in the funding models for the different programs, which is not unexpected given the diversity of the health systems represented. A national health system by its nature would test funding mechanisms that are quite different from those of a local health system in the United States that derives income primarily from fee-for-service activities. However, it is evident that none of the programs have developed a robust model of sustainability. Most depend on some combination of funding from the institution (or government), philanthropy, grants and contracts, and in-kind contributions to subsidize sequencing costs. Early-stage implementation is evidenced by most programs not charging patients to participate or using a clinical research model to ensure that there are no out-of-pocket costs, at least for the testing and initial consultations. In the US programs, patient participants are transitioned to usual clinical care, with its associated costs to patients and third-party payers.

Several of the US projects are testing models that reflect local coverage and reimbursement practices. The Geisinger and University of Vermont programs have partnered with provider-owned health plans to begin to explore the value of genomic population screening from the insurer's perspective. The Penn Medicine and NorthShore/Sema4 projects are using a concierge

fee-for-service medicine approach to more directly ascertain the value of these services to patients. Recognizing that this approach is likely to promulgate the current inequities in availability that have skewed participation in most cases toward individuals with higher educational attainment and socioeconomic status, the NorthShore/Sema4 project is subsidizing testing in a setting that cares for underserved patients. No results are available to assess the success of such an approach. Further research into the sustainability of these programs is needed, much of which will be dependent on robust evidence of clinical effectiveness, as discussed in Section 4.2.

4.4. Cost-Effectiveness

Cost-effectiveness analyses can be an important part of policy decision-making. This is especially true in countries other than the United States, where a cost-effectiveness analysis is frequently incorporated along with outcomes and other evidence into the decision-making process to add new services into the national health system. While none of the programs described specifically included a cost-effectiveness analysis as part of the implementation, outcomes from the programs have the potential to inform the model assumptions to reflect real-world conditions and provide a more realistic grounding for the analyses. An early example of this comes from a publication by the Rational Integration of Clinical Sequencing (RISE) project that examined the cost-effectiveness of population screening for HBOC (22). This study used outcomes data from the MyCode Community Health Initiative to provide additional validation to model assumptions derived from the literature or expert consensus. The project is applying the same approach to the study of cost-effectiveness to Lynch syndrome and familial hypercholesterolemia. As more robust outcomes data become available from genomic population screening programs, the cost-effectiveness models will be better able to reflect real-world implementation, thus becoming of more value to decision-makers.

4.5. Limitations

The PubMed search strategy yielded some relevant papers but missed others. Some were identified through the similar-articles function or review of reference lists. Others were identified through other strategies. Notably, the MeSH terms applied to the relevant articles are relatively nonspecific (e.g., Delivery of Healthcare; Genetic Testing; Genetics, Population; Genotype; and Mass Screening/methods), meaning that this strategy was not as effective as anticipated.

The major limitation to this review is the paucity of peer-reviewed and published information available on the relevant programs. This is not unexpected, in that, with a few exceptions, most of these programs have only started within the last two years. This necessitated more reliance on program websites, news releases, and other information rather than published literature. The information provided is variable and does not always address the points of interest of this review. Sites that are aggregating information on population cohorts, such as the IHCC's, are not explicitly annotating the type of genomic testing used or whether results are being returned to participants. To mitigate this potential weakness, additional information was sought from the IHCC coordinating center, and project websites were reviewed from the URLs provided at the IHCC website (24) and by the systematic review. Despite these efforts to be comprehensive, it is possible that this strategy missed some relevant programs.

5. CONCLUSION

Population screening programs based in healthcare systems are beginning to be implemented. The diversity of approaches provides opportunities to learn and better understand the optimal

approach to implementation based on the contextual setting. This could be accelerated by standardizing outcomes of interest and aggregating data through groups like the IHCC or similar organizations. Emphasis on reuse of sequencing information generated by population screening programs over the course of a patient's lifetime could enhance the value of this approach.

DISCLOSURE STATEMENT

The author is an employee of Geisinger but receives no funding specific to either the Geisinger MyCode Community Health Initiative or the Geisinger DNA screening program. The author is the current president of the ACMG but is not acting in this capacity or representing the organization for the purposes of this review.

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