

# **Overview and Update of Population Genetic Screening of Actionable Genes in the United States**

by

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# Overview and Update of Population Genetic Screening of Actionable Genes in the United States

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University of Pittsburgh, 2022

## Abstract

**Background:** With the advancement in the knowledge of genetics and the emergence of evidence-based recommendations, genomic/genetic screening of adult-onset genetic conditions in healthy adults has gained attention in the past decade. Population genetic screening provides the opportunity to identify high-risk individuals within the general population regardless of medical indications. To date, no central database exists for population genetic screening programs. Research programs offer screening for actionable genetic conditions by referencing some guides provided by professional organizations, which were not intended for population screening application. This study aims to identify existing programs and create a patient-friendly educational resource about the existing programs that are actively enrolling participants.

**Methods:** The list of programs was first obtained using Foss et al. (2022), followed by a review of CDC's State Public Health Genomics Program Map and online searches of each state. The website was created on Wix, a cloud-based development platform. The Flesch–Kincaid readability test was used to assess website readability.

**Results:** In addition to the *All of Us* Research Program, the study identified a total of 17 population genetic screening programs in the United States. Many programs are clustered either in the western states or the eastern states, leaving a gap in the middle and northern west states. This was also true for the enrollment sites for the *All of Us* Program. The website, a patient-friendly educational resource, included overviews of genetics, population genetic screening, common

population screening conditions, and existing population genetic screening programs. The website scored 8.2<sup>nd</sup>-grade reading level.

**Conclusion:** This study is one of the first efforts in identifying a comprehensive list of population genetic screening programs across the United States. The educational resource developed provides novel information to the public, which will continue to grow in importance as more opportunities for the public to participate in population genetic screening programs become available.

**Public Health Significance:** This study contributes to public health by addressing one of the 10 essential services of public health: linking people to appropriate health services. Creating a patient-friendly tool that helps identify the programs can help initiate patients to participate in population screening programs.

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## **1.0 Background**

In 2003, the Human Genome Project was completed and revealed the sequence of the human genome. This event drastically shifted the clinical and population health application of genetic information, which now includes the availability of whole exome/genome sequencing and the establishment of evidence-based practice guidelines and web-based resources for diseases and pharmacogenomics (Evans et al., 2011; Manolio & Green, 2011; Wei et al., 2013).

For many years in the United States, newborn screenings have been the only public health programs that placed their focus on the reduction of morbidity and mortality by the early identification of genetic conditions (Bowen et al., 2012). However, with the advancement in the knowledge of genetics and the emergence of evidence-based recommendations, the possibility of genomic/genetic screening of adult-onset genetic conditions in healthy adults has gained attention in the past decade. Direct-to-consumer testing products such as 23&Me have existed for more than a decade to offer testing to proactive individuals who are interested in knowing more information about their health risks; however, there are significant limitations associated with the information gained from these tests. Those results typically involve polygenic risk scores, the presence of common polymorphisms, and carrier statuses. High-risk Mendelian diseases, in contrast, have historically been limited to individuals who meet the testing criteria (Khoury et al., 2022). Studies have suggested that about 1-2% of individuals in the United States carry a pathogenic variant that elevates the risk of developing a serious yet preventable disease (Evans et al., 2013; Evans et al., 2017). Screening could provide an opportunity to identify these high-risk individuals and reduce the events of unfavorable outcomes caused by undiagnosed diseases (Murray et al., 2018).

Population screening can be divided into two distinct categories: proactive screening and opportunistic screening (Australian Law Reform Commission, 2010; Murray et al., 2018). Proactive screening systematically identifies the individuals who have asymptomatic disease and risks for future disease or adverse drug outcomes, providing the opportunity for earlier treatment or mitigating future risks. This may include newborn screening, carrier screening, population genetic screening, etc. Proactive screening may be conducted with unselected populations or selected populations such as high-risk individuals. Opportunistic genetic screening would identify an unsuspected disorder or secondary genetic testing results when an individual has genetic tests for other medical reasons. The recommendation provided by the American College of Medical Genetics and Genomics (ACMG) to report the secondary findings under clinical exome/genome-sequencing is an example of opportunistic screening (Miller et al., 2021).

When implementing screening programs, it is important that workgroups of experts in the field consider the feasibility, cost-effectiveness, clinical utility, and benefit versus harm measures. As it is evident that current knowledge and technology cannot interpret genome-wide data for application in general population health, the current clinical focus of public health genetics programs is to conduct more targeted testing of well-studied genes that have clinical relevance and offers more benefit than harm (Murray et al., 2018). Implementation of genomic/genetic screening programs, which most commonly are still occurring in a research setting, not only provides opportunities for information-seeking individuals to receive genetic testing, but also provides an opportunity to investigate the clinical utility and efficacy, community acceptability, and economic impact of screening in unselected healthy individuals (Khoury et al., 2022).

## **1.1 Organizations Referenced for Population Screening Actionable Genes**

As population genetic screening is an emerging field, with most initiatives occurring in the research setting, there are no established recommendations or guidelines that exist to guide population screening programs. However, these population screening research programs often reference lists of conditions/genes that have been developed by two primary organizations: the Centers for Disease Control and Prevention (CDC) and the American College of Medical Genetics and Genomics (ACMG). Although conditions/genes included by these organizations are not specifically made for the usage of population screening programs, many programs reference these lists due to emerging evidence of their clinical utility and the existence of follow-up guidelines.

### **1.1.1 CDC Tier Classification**

CDC's Office of Genomics and Precision Public Health (OGPPH), formerly known as the Office of Public Health Genomics, had initially established a classification table of genomic tests and family history applications using the method utilized by Clinical Pharmacology and Therapeutics published in 2014 (Dotson et al., 2014). The tier table, now converted to a guideline database, organizes guideline publications via levels of evidence, with the tier codes indicating the quality of evidence for the highest tier level achieved in a given set of guidelines. The CDC OGPPH provides three application classifications: Tier 1 (Green), Tier 2 (Yellow), and Tier 3 (Red). Tier 1 applications have evidence to support implementation in routine practice; Tier 2 applications lack the evidence to support implementation in routine practice, yet evidence suggests usefulness in decision making of clinical practice or public health policy; Tier 3 applications may

have evidence against implementation or may not have relevant evidence (Dotson & Khoury, 2018; Dotson et al., 2019).

The CDC OGPPH has decided to place its focus on three Tier 1 genomic applications, including Hereditary Breast and Ovarian Cancer syndrome (HBOC), Lynch syndrome (LS), and Familial Hypercholesterolemia (FH) (CDC OGPPH, 2014). Despite the fact that approximately 2 million Americans have pathogenic variants that cause HBOC, LS, or FH, many individuals are unaware of their increased risks. Thus, early detection of the conditions is the key to helping reduce morbidity and mortality of these genetic diseases. CDC has created a toolkit for these three Tier 1 genomic applications, comprised of two phases. Phase 1 implementation generally discusses strategies to identify index cases by screening high-risk populations. Phase 2 implementation involves developing approaches to cascade screening. The toolkit can help state/local public health organizations and healthcare providers/payers to quickly learn about these conditions and potential opportunities for partnerships when implementing programs (CDC OGPPH, 2014).

Although their recommendation is not established for the application to the general population, some screening programs partner with commercial laboratories to screen for these CDC Tier 1 conditions. For example, NorthShore HealthSystem, Oschner Health, and UCSF Preventative Genomics Clinic partner with Color health Inc, and Healthy Nevada Project and Medical University of South Carolina's In Our DNA partner with Helix (Foss et al., 2022).

### **1.1.2 ACMG Secondary Findings**

ACMG originally published a guideline in 2013 of a list of genes where actionable mutations should be reported as secondary findings (SF) to guide clinical laboratories about genes to report back to patients when clinical exome and genome sequencing are performed for other

indications. The ACMG Secondary Findings Maintenance Working Group (SFWG) evaluates the actionability, penetrance, and burden of available treatment/management to patients, maintaining the balance between the patients' interests and extra demands placed on laboratories. The original guideline included 56 genes, with conditions including HBOC, LS, FH, Marfan syndrome, cardiomyopathy, retinoblastoma, and others (Green et al., 2013). The guideline was updated in 2016 (v2.0) and 2021 (v3.0); it now includes 73 genes covering various phenotypes from cancer, cardiovascular, and metabolic conditions (Kalia et al., 2017; Miller et al., 2021).

The statement from ACMG explicitly states that these genes are not validated for general population screening and strongly discourages the application outside of the intended utility as secondary findings (Directors, 2019). Despite a lack of validity, some research projects (e.g., All of Us Project) and clinical laboratories (e.g., Fulgent Genetics and Invitae Corporation) offer to test for these actionable genes as proactive screening (All of Us Research Program, 2021; Fulgent, n.d.; Invitae, n.d.). Research programs that are offering to screen for ACMG SF list can help learn more about the clinical utility and validity of screening for actionable genes in the general population.

## **1.2 GPHAC Tier Classification and Screening Recommendation**

In 2017, an activity of the Roundtable on Genomics and Precision Health of the National Academies of Sciences, Engineering, and Medicine called the Genomics and Population Health Action Collaborative (GPHAC) formed the Population Screening Working Group (PSWG). The PSWG focused its work on genomic-based screening in healthy individuals, developing its own two-tier classification system. The PSWG classified HBOC (*BRCA1/2*), LS (*MLH1*, *MSH2*,

*MSH6*, *PMS2*, and *EPCAM*), and FH (*LDLR*, *APOB*, and *PSCK9*) into their Tier 1 classification, given their high penetrance, clear disease causation, and established interventions that are effective in reducing disease/disease risks. While other conditions in the ACMG SF list were considered by PSWG, they were excluded from population screening recommendations due to their lack of evidence to support population screening. Tier 2 classification criteria, therefore, are genes that have unknown/low penetrance and less understanding of phenotype, while effective intervention and follow-up confirmatory testing are available. Examples include *PALB2*, hereditary hemochromatosis, malignant hyperthermia, hypertrophic cardiomyopathy, long QT syndrome, and pharmacogenomic variants (Murray et al., 2018).

The PSWG has concluded that the risks outweigh the benefits brought by population screening in healthy individuals for most conditions at this time due to a lack of knowledge of the natural history of most genetic conditions and a lack of ability to accurately interpret genomics data. A targeted approach would be more appropriate to be conducted in a research setting. It concluded that only the three CDC Tier 1 conditions (HBOC, LS, and FH) appear to be appropriate to be screened in a healthy population (Murray et al., 2018).

### **1.3 Benefits and Challenges of Population Genetic Screening Programs**

Some challenges faced by the implementation of population genetic screening programs include a proper informed consent process, result disclosure, and equity. Considering the current available genetic counselor workforce, portions of consent and return of results processes would need to be performed by non-genetics providers. Thus, the establishment of protocols for the steps

involved with population genetic screening would be critical as programs are implemented (De Simone et al., 2021).

Despite the increasing evidence and acceptance of the approach of identifying index cases by screening high-risk populations for cancer and cardiovascular disease, studies have also shown that a significant proportion of individuals are left undiagnosed with the current screening modality. For example, a study that conducted exome-sequencing screening on over 5,000 individuals has shown that among patients who were diagnosed with HBOC, approximately 16% (44/267) did not meet the clinical testing criteria for HBOC. The same study showed that 82% (219/267) of individuals who tested positive had no prior clinical testing (Manickam et al., 2018). Similarly, it is estimated that approximately 25% of individuals with LS have no family history or personal history and are left unrecognized (Everett et al., 2014; Landon et al., 2015; Lynch Syndrome Screening Network, n.d.; Win et al., 2013). As population-based genetic screening conducts genetic testing in unselected healthy individuals, it can alleviate the uptake and sensitivity limitations faced by history-based screening and offer better opportunities to prevent diseases.

However, there are a number of knowledge gaps in population genetic screening that need to be addressed before implementation beyond the scope of research. Research projects must continue to provide information on optimal genes, the age of the population, and engagement strategies (Murray, 2018). The natural history of diseases, their prevalence and penetrance in the general population, the sensitivity/specificity of the test, ability of interpretation, and management/treatment availability are all factors that need to be considered when deciding which genes to be included in the screening. Lack of this knowledge may lead to either under-/overtreatment or management. Optimal ages of testing can differ depending on the genetic condition. Conditions like FH may require intervention from childhood, while interventions for



many adult-onset cancer predisposition conditions such as HBOC and LS do not start until the early- to mid-20s (Idos & Valle, 2004 [Updated 2021]; Petrucelli N et al., 1998 [Updated 2022]; Youngblom E et al., 2014 [Updated 2016]). It may not be appropriate to test for all available actionable genes at a single age. Pre-/post-test counseling is a critical component of genetic testing, yet population screening only increases the demand for finite genetic professional recourses. Implementation strategies such as a systematic intervention or increasing the volume of trained non-genetics professionals that facilitate these processes to meet the demand would be important to appropriately conduct informed consent and result disclosures (Murray, 2018).

Furthermore, determining the economic impact of population screening must be considered. The comparison of costs in allocating scarce resources, costs involved with follow-up preventative treatments, and short-term/long-term outcomes of life-years saved to the existing screening programs need to determine the clinical value of population screening. As population screening impacts a wide range of individuals in the public, learning how to address ethical considerations in protecting patients' autonomy, privacy, right not to know, and beneficence while bringing equal benefits to all individuals is critical (Murray, 2018).

#### **1.4 Existing Population Genetic Screening Programs**

The *All of Us* Research Program is a nationwide project funded by the National Institutes of Health (NIH). The program set its goal to enroll one million participants living in the United States in order to establish a highly diverse health database that will help researchers understand the impact of biological and environmental factors on health. As of May 24, 2022, more than 689,000 individuals have registered through online accounts, and approximately 339,000

participants have completed the initial process of the program. Initial steps include the consent process, agreement to share the electronic medical record, and the completion of the initial surveys (All of Us Research Program, 2022).

Any individual who are 18 years of age or older, living in the United States, able to provide consent by themselves, and not in prison can participate in *All of Us* (All of Us Research Program, n.d.-c). Currently, there are 62 enrollment sites across the nation. The enrollment sites, also known as Health Care Provider Organizations (HPOs), can help participants learn more about the *All of Us* Research Program and join (All of Us Research Program, n.d.-a). Individuals who do not have the HPOs nearby can also enroll in the program online through the National Direct Volunteer Program (All of Us Research Program, n.d.-b). The *All of Us* Research Program project plans to screen for and return the results of 59 actionable genes defined by ACMG SF v2.0 (Abul-Husn et al., 2021).

Although there are population genetic screening programs across the United States beyond the *All of Us* Research Program, little is known about the landscape of screening programs as no central database exists to help organize existing screening programs. Some organizations/programs reference CDC Tier 1 applications or ACMG secondary finding lists to decide what genes to include on their list. This essay project aims to identify programs across the United States and to determine which actionable genes are offered to be tested by each program.

## **1.5 Program Outcomes**

It is important to employ the essential components of public health when implementing population screening programs and trying to eliminate the health disparities, which includes

population assessment and disease surveillance, evidence-based policy/guideline implementations, and assurance of access to services and education through continual evaluation and improvement of interventions (Khoury et al., 2022). Proactive population genetic screening for actionable genes aiming to prevent and detect disease early has gained its attention yet it is not widespread as discussed in the previous section. As the identification of patients with monogenic disorders has historically been among individuals with a family and/or personal medical history who meet the testing criteria, the knowledge of the natural history, penetrance, and the prevalence of these diseases within a healthy population is still evolving. Haverfield et al. (2021) conducted a large multi-center cohort study, published in 2021, that involved 10,478 unrelated adults and screened for 147 genes that are associated with Mendelian disorders beyond the ACMG SF list and CDC Tier 1 conditions. The study examined the efficacy of offering multi-gene panel screening by specialists and primary care providers. It identified ACMG SF list pathogenic variants in 3.1% of individuals and three CDC Tier 1 conditions in 2.0% of individuals, overall demonstrating a positive test rate in 6.2% of participants, including hereditary cancer syndromes, cardiovascular diseases, or malignant hyperthermia risks (Haverfield et al., 2021). In 2020 articles, both Geisinger's MyCode project and the Healthy Nevada Program determined that population screening can diagnose individuals with three CDC Tier 1 conditions that would not have been otherwise identified using current testing criteria (Buchanan et al., 2020; Grzymski et al., 2020). These studies speak to the benefits of incorporating genetic screening as routine medical care.

Studies like Haverfield et al. (2021) reported a higher prevalence of three CDC Tier 1 conditions than previously estimated for the general population (overall rate of 1 in 51 in Haverfield et al. vs 1 in 148 previous estimates). Alabama Genomic Health Institute (AHGI) also recently reported that variants related to cardiovascular disease have lower penetrance than

previously estimated in the general population (East et al., 2021; Haverfield et al., 2021; Murray, 2018). Further studies should measure the rates of disease development in individuals with positive testing who are yet to have symptoms.

The assessment of cost-effectiveness is another essential measure when implementing population screening programs. Despite the current lack of long-term cost and benefits evaluations, some economic evaluation studies have reported the potential cost-effectiveness of providing free/reduced-cost screening for certain actionable genes. A study has shown that HBOC population-wide genomic screening may be cost-effective among younger females when compared to family history-based screening. Their model demonstrated that the incremental cost-effectiveness ratio (ICER) of population-wide screening in 30-year-old women was \$87,700 with a 78% probability of being cost-effective at the \$100,000 per quality-adjusted life-year (QALY) threshold. Whereas population-wide screening in 45-year-old women demonstrated the ICER of \$268 200, which has a 0% probability of being cost-effective (Guzauskas et al., 2020). Similarly, LS population-wide genomic screening may be cost-effective in a younger population when compared to family history-based screening. Screening in unselected 30-year-olds for LS showed the ICER of \$132,200, which has a 71% probability of being cost-effective under a \$150,000 per QALY threshold. However, only an 8% probability of being cost-effective under a \$100,000 per QALY threshold (Guzauskas et al., 2022). A cost adaptation analysis conducted on the cost-effective analysis of FH population-wide screening in young Australian adults suggested that FH genomic screening may also be cost-effective in the United States (Marquina et al., 2021). More studies need to investigate the utility of universal genomic screening in wide age ranges and various backgrounds in various genetic conditions being considered to be screened for as actionable genes.

### **1.5.1 Consent**

Providing appropriate informed consent to participants before enrolling in screening programs or biobanks is an essential component of current population screening studies. The proper consent must include specific aims of the study, possible risks and benefits, as well as the nature of “unknowns” arising in the future as part of cutting-edge/exploratory research. Not only the scope of the research programs, but also privacy protections and concerns for discrimination including GINA must be covered prior to genetic screening (Doerr et al., 2019). The *All of Us* Research Program decided to take its form consent in video modules, explaining different parts of the program consent succinctly with visual aids in short videos (Doerr et al., 2019). As mentioned previously, many other local population screening programs’ enrollment is conducted by primary care providers. Assessment of whether thorough consent addressing the complex nature of population screening and biobanking is provided to participants during limited patient-provider time must be conducted.

### **1.5.2 Return of Results**

How the return of result is made to the participants are also a rising debate, including the methods of receiving the results, the opportunity to opt in, out, or pause to receive the result when the results become available, and whether negative results are returned to the participants. BioMe Biobank at Mount Sinai reported that 60% of participants preferred to receive their results from either a genetic counselor or a medical geneticist, whereas 15.7% answered that they prefer results to be returned by a primary care physician. Fifty percent of these participants also indicated that their preferred method of receiving the results is by letter (Abul-Husn et al., 2021). Furthermore,

the return of positive test results has further implications to be clinically useful. An investigation was conducted on the Healthy Nevada Project, which is supported by Renown Health, the largest healthcare network in northern Nevada. This study showed that among individuals who tested positive for one of the three CDC Tier 1 conditions and who responded to the survey, 71% of participants shared their findings with their healthcare provider, yet only 22% had genetic diagnoses appearing on the electronic health records (EHRs) at Renown Health, and only 10% appearing on their problem list. Ongoing training of healthcare providers on the documentation of the findings and subsequent clinical care is another emerging pursuit in the field of population screening (Elhanan et al., 2022).

While participants with positive results commonly receive an opportunity to be seen by genetic counselors, individuals with negative results often have results delivered through a very brief and/or templated summary, creating opportunities for false reassurance and misinterpretation of the nuances surrounding negative results (Butterfield et al., 2019). In the GeneScreen study, associated with the University of North Carolina-Chapel Hill and Kaiser Permanente Northwest biobank, over 45% of individuals answered the post-negative result survey incorrectly. Of 249 (95%) participants who received negative results via email, 44.3% individuals answered that they do not have mutations, unwittingly ignoring the possibility of false-negative results; approximately 1.5% (n=2) individuals believed that they are still likely to have mutations despite the negative results (Butterfield et al., 2019). This study spotted the importance of not only placing the value on returning positive results, but also considering and evaluating an efficient and effective way of returning negative results.

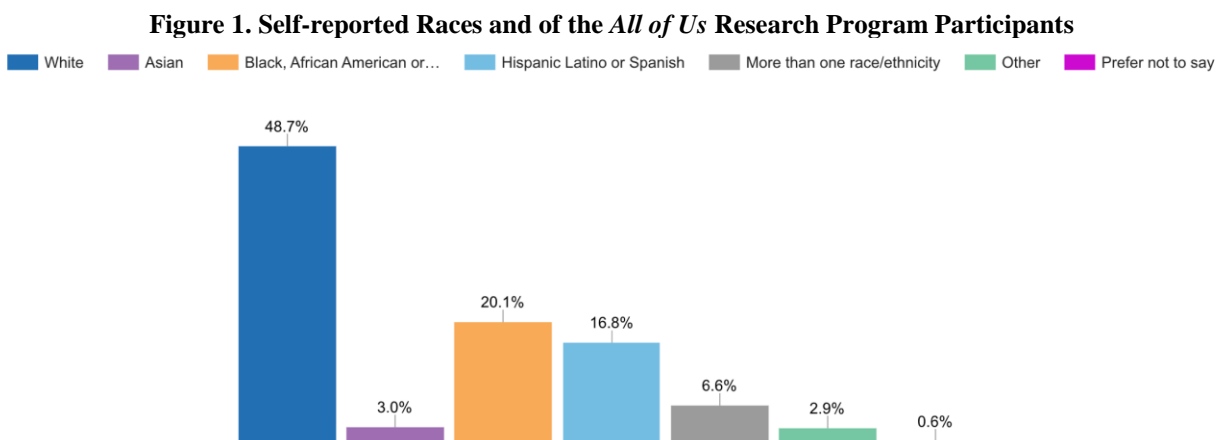
### 1.5.3 Diversity and Equity

In any scientific research, including genetics and genomics research, the inclusion of a diverse population is essential in obtaining novel insights into health disparities, understanding human biology, and improving clinical care. However, scientific research has historically been conducted primarily in white individuals and racial and ethnic minority populations have been underrepresented (Bentley et al., 2017).

While some research programs remain predominantly focused on White European individuals, some efforts in addressing the underrepresentation of other racial and ethnic groups have been made by various population genetic screening programs. For instance, over 65% of BioMe Biobank at Mount Sinai research participants identified themselves as a member of a racial or ethnic minority group (The BioMe Biobank at Mount Sinai, n.d.). The Sangre Por Salud (SPS) Biobank project by Mountain Park Health Center (MPHC) in conjunction with Mayo Clinic conducted their study to facilitate genetic research on the Latino population in the Maricopa County area (Shaibi et al., 2016). Alaska, as another instance, does not have a university-based medical center, cytogenetics or genetics laboratory, or pediatric clinical geneticist (Western States Regional Genetics Network, n.d.). In the field of research, Alaska Natives and American Indians (ANAI) have a history of mistreatment and underrepresentation. Studies that address the perception of ANAI individuals and the ways to mitigate mistrust between the research communities and ANAI community are critical, including genetics research programs. Many studies have demonstrated the community expectation that ANAI members be engaged throughout the entire research project beyond just during the recruitment and result dissemination (Beans et al., 2018; V. Hiratsuka et al., 2012; V. Y. Hiratsuka et al., 2012). A small public deliberation study involving 19 individuals ranging from 22-63 years of age exhibited community members' ability

to thoroughly examine and discuss considerations needed for testing and return of results involved with genetic research despite not having formal training in genetics and ethics. This study also revealed participants' clear interest in potential benefits brought by genetic testing to make an informed decision about their health, and efforts in closing these gaps are critical to mitigate the disparity as such decision would be made against their historical backdrops of collaborative harms (Hiratsuka et al., 2020).

The participants of the *All of Us* program also remain predominantly White individuals: slightly less than 50% and no representation of ANAI individuals as its own group (Figure 1) (All of Us Research Program, 2022).



The graph represents the percentage of participants' self-reported race and ethnic background who completed the initial steps of the program, obtained from the *All of Us* Data snapshot website: <https://www.researchallofus.org/data-tools/data-snapshots/>. The *All of Us* project does not have ANAI individuals represented.

The federal effort, the *All of Us* program, as well as other genomics screening programs have room to improve and place continuous efforts to address issues with diversity, inclusion, and equity. Considerations include the identification and elimination of systemic barriers, the inclusion



of stakeholders from underserved communities, and re-evaluating the frameworks for screening guidelines and recommendations with perspectives of minority groups (Azriel et al., 2022).

Although population genetic screening is still occurring on a research basis, opportunities exist for information-seeking individuals to participate in research and to learn about their health risks. This essay project aims to identify population screening programs and what conditions they screen for, as well as to create patient-friendly education material to help facilitate the public to learn about such opportunities.

## 2.0 Materials and Methods

### 2.1 Investigation of Population Genetic Screening Programs

A list of population screening programs in the United States was constructed from a literature and internet search. A list of population screening programs identified by Foss et al. published in April of 2022 was used as a starting list for this project (Foss et al., 2022). This article reviewed online resources and scientific literature to identify the programs that implemented population screening for various actionable genes, including those associated with CDC Tier 1 conditions and those on the ACMG secondary findings list. This publication identified 12 population genetic screening programs, almost equally split between academic and health care institutions. The programs reviewed by Foss et al. (2022) are summarized in Table 1:

**Table 1. Summary of Population Genetic Screening Programs by Foss et al. (2022)**

Programs	Enrollment Status	Screening
<b>System-wide Program</b>		
Geisinger MyCode, Danville, PA	Active	ACMG SF v2.0
Northshore DNA10K, Chicago, IL	Inactive	ACMG SF v2.0
Ochsner Health innovationOchsner Population Genomic Screening Program, New Orleans, LA	Unknown	CDC Tier 1
Sanford Health The Sanford Chip, Sioux Falls, SD	Active	ACMG SF v2.0
Stanford University Humanwide, Palo Alto, CA	Inactive	CDC Tier 1
University of California at San Francisco (UCSF) 3D Health, San Francisco, CA	Active	ACMG SF v2.0
University of Vermont the Genomic DNA Test, Burlington, VT	Active	ACMG SF v2.0
<b>Statewide Program</b>		
Alabama Genomic Health Initiative (AGHI), UAB Medicine, AL	Active	ACMG SF v2.0
Healthy Nevada Project, Renown Health, NV	Active	CDC Tier 1
<b>Clinic-Based Programs</b>		
Brigham & Women's Hospital Preventive Genomics Clinic, Boston, MA	Active	Clinical lab proactive panel

St. Elizabeth Healthcare Precision Medicine and Genetics, Edgewood, KY	Active	Clinical lab proactive panel
UCSF Preventive Genomics Clinic, San Francisco, CA	Active	Clinical lab proactive panel

Out of 12 programs discussed by Foss et al. (2022), nine programs are actively enrolling patients, one program's enrollment status is unknown, and two ended their recruitment (Foss et al., 2022).

Additionally, CDC's State Public Health Genomics Program Map was reviewed to screen for additional programs (CDC PHGKB (v7.7), n.d.). Subsequently, online searches for each state were done on Google to capture population genetic screening programs that were left unrecognized. The search terms include "population genetic screening," "actionable," and "biobank," in addition to the name of the state. The Google searches were conducted between May 19 to 22, 2022.

After the initial list of programs was generated, exclusion criteria were applied prior to finalizing the list of active programs. The exclusion criteria included precision medicine biobanks or population genetic screening programs that closed their enrollment or did not specify that they are returning actionable gene testing results to their participants. Examples include [Biobank Mississippi](#) and [UCLA Precision Health Biobank](#). The programs that had an unknown status of enrollment were kept on the list.

## 2.2 Patient-Friendly Educational Website

As there is no central database online that discusses all population screening programs, website creation was selected as an online resource for the public. Wix, a cloud-based development platform, was utilized to create the website ([wix.com](https://www.wix.com)). Free images were obtained from

hiclipart.com, vecteezy.com, and pexels.com to design the website as well as to provide visual aids to the readers. The contents of the webpages are constructed in the order of basics to more complex information – from the definition of genetics and population genetic screening, conditions covered, to the programs available across the states. The conditions page utilized information published by the CDC Tier 1 genomic applications and the ACMG SF list. The existing programs page compiles the results obtained from the Google search.

### **2.3 Readability Assessment**

The paragraphs from the website were transferred to a word document in order to obtain the reading level using Flesch–Kincaid readability tests.

### **3.0 Results – Patient-Friendly Resource**

A patient-friendly online resource was created to educate the general population about population screening programs. The website can be accessed using the following URL: <https://aim331.wixsite.com/populationscreening> (password: PittMPH\_essay). The website contains a home page that includes a basic genetics overview, a second page that briefly explains population genetic screening, a third page that reviews the recommended conditions for population screening and its limitations, and the last page provides an overview of existing population genetic screening programs.

#### **3.1 Home Page**

The home page has buttons that lead to other pages: population genetic screening, conditions, and existing programs (Figure 2). This page also includes fundamental genetics information to provide baseline information for the additional materials on the website. On the homepage, the terms genetics, DNA, chromosome, genes, and mutation/pathogenic variant are defined.

**Figure 2. Patient Education Resource – Home Page**

[Home](#) [Population Genetic Screening](#) [Conditions](#) [Existing Screening Programs](#)



Population Genetic Screening  
**Find Your Genetic Risks to Prevent Diseases**

1-2% of people in the United States have a genetic risk that causes a serious disease (e.g., cancer & heart disease) [1, 2].  
Knowing your genetic profile may help you prevent those future risks.



Population Genetic Screening



Conditions



Existing Programs

## What is Genetics?

Genetics is a study of genes and inheritance – how we pass on traits from parents to a child.

DNA is our genetic material.

Inside each of our cells, chromosomes tightly package the DNA to store genetic information.



Sections of DNA are genes. Each gene gives a unique instruction to our body on how to grow and function. Having a harmful change in a gene (mutation/pathogenic variant) can lead to disease if the gene no longer works.



Each person gets half the genetic material from the mother and the other from the father. This means that each gene also comes in a pair.

Having a gene mutation can increase your risk to develop certain diseases like cancer or heart disease. You can do genetic testing to find out if you carry those risks.

[Learn More about Population Genetic Screening >](#)

## 3.2 Population Genetic Screening

This page provided a definition, a brief overview of population genetic screening, and the potential reasons to undergo such testing (Figure 3).

**Figure 3. Patient Education Resource – Population Screening Overview**

### What is Population Genetic Screening?

It is a systematic process that tests certain genetic diseases in a general population.

On this website, we define population genetic screening as:

“Genetic testing that screens healthy people for diseases that can affect them later in life.”

Examples include predisposition to cancer, heart disease, etc.

Knowing your genetic risks can guide your care.

You can be proactive about screening and treatment.

If you carry a genetic mutation, you can let your family members know. This way, they can also do testing and try to prevent/treat the disease.

This knowledge can also help with your reproductive decisions.



[Learn More about Example Screening Conditions >](#)

## 3.3 Conditions

In this section, common conditions and two organizations (CDC and ACMG) that are often referenced by the population screening programs are covered (Figure 4). It goes over HBOC, LS, and FH as the focus of CDC Tier 1 genomic applications (CDC, 2016, 2022a, 2022b). The interactive boxes for these conditions have a “Read More” button that leads to the CDC page that explains these conditions more in detail (CDC, 2016, 2022a, 2022b). Different versions of ACMG

SF lists are covered on this website since the number of genes that they include are variable and different programs use different versions of the ACMG SF list for their research (All of Us Research Program, 2021; Green et al., 2013; Kalia et al., 2017; Miller et al., 2021).

**Figure 4. Patient Education Resource – Conditions Page**

## Conditions

Population screening programs offer to test for different genetic conditions. Programs commonly reference two organizations when selecting genes to screen for. Many of the conditions are common in the general population. There are guidelines to follow if we find a genetic mutation. Guidelines will help prevent the disease or treat the disease at an earlier stage.

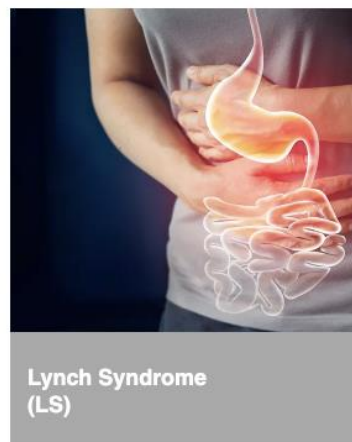
### Centers for Disease Control and Prevention (CDC)

CDC has recommendations in a tier classification: Tier 1 to 3. Tier 1 conditions have established evidence and suggest clinical use.

CDC has a focus on three Tier 1 applications:

- **Hereditary Breast and Ovarian Cancer Syndrome (HBOC)** [1] – cancer predisposition
- **Lynch Syndrome (LS)** [2] – cancer predisposition
- **Familial Hypercholesterolemia (FH)** [3] – cardiovascular disease

Click to learn more about each condition:



### American College of Medical Genetics and Genomics (ACMG)

ACMG secondary findings (SF) list has genetic conditions recommended for screening when people undergo genetic testing for other purposes. [4]

ACMG recommendation has a few versions:

- Version 1 (2013): **56 genes** (ACMG SF)
- Version 2 (2016): **59 genes** (ACMG SF v2.0)
- Version 3 (2021): **73 genes** (ACMG SF v3.0)

These lists include genes that can lead to diseases like cancer, heart and blood vessel diseases, metabolic diseases, and others. This includes HBOC, LS, and FH. [5, 6]

Some population research programs (e.g., *All of Us*) & genetics laboratories offer to test for ACMG recommended conditions. [7]



### 3.3.1 Why Should I Consider Genetic Screening?

This section identifies some benefits, limitations, and risks of undergoing population genetic screening in the research setting. The goal of this page is to educate people about considerations before signing up for a population screening program (Figure 5) (CDC, 2016, 2022a, 2022b; CDC OGPPH, 2014). This will especially be useful for individuals who may not have programs/recruitment sites nearby to speak with enrollment personnel about the pros and cons before enrolling in those programs.

**Figure 5. Patient Education Resource – Conditions Page: Why Should I Consider Screening?**

#### Why Should I Consider Screening?

These conditions are fairly common in the general population.  
For example, about 2 million people in the United States have either HBOC, LS, or FH. [9]

In the general population, approximately...

- 1 in 400 - 500 people has HBOC
- 1 in 300 people has LS
- 1 in 200 - 250 people has FH [10, 11, 12]

You may not have a family history or personal medical history.  
For example, about 25 % of people with LS are thought to have no family history or personal medical history. [13]

Therefore, even without histories of disease, having genetic screening can help mitigate your future health risks.

Knowing your genetic risks and the inheritance, you may help your family members with their risks too!

#### Limitations

Population screening is still in the research stages.  
We may have a good understanding of these conditions in people with diseases, but not in a healthy population. We especially have limited genetics knowledge in the underrepresented minority population.

Keep in mind that...

- genetic screening does not test for every health condition. Each gene screened corresponds to one genetic condition/trait.
- many of these programs are in research settings. If your result comes back positive, a clinical laboratory needs to confirm your result.
- many of these research programs store your DNA information for different uses than a health risk screening. For example, they may use your DNA and electronic medical records to find new disease associations. Ask the program for more detail.

#### GINA

The **Genetic Information Nondiscrimination Act (GINA)** is a federal law made in 2008  
The law protects you against the discrimination by

- **health insurance:** insurance companies cannot deny health insurance or decide on coverage based on genetic test results
- **employer:** company (with >15 employees) cannot make any employment decisions (like hiring, firing, or promoting you) based on the genetic test results

This law does not protect you from obtaining new life insurance, disability insurance, or long-term care insurance. If you apply for any of these insurances, they can ask you about genetic information and decide on your coverage.

[Learn about Existing Programs >](#)

### 3.4 Existing Population Screening Programs

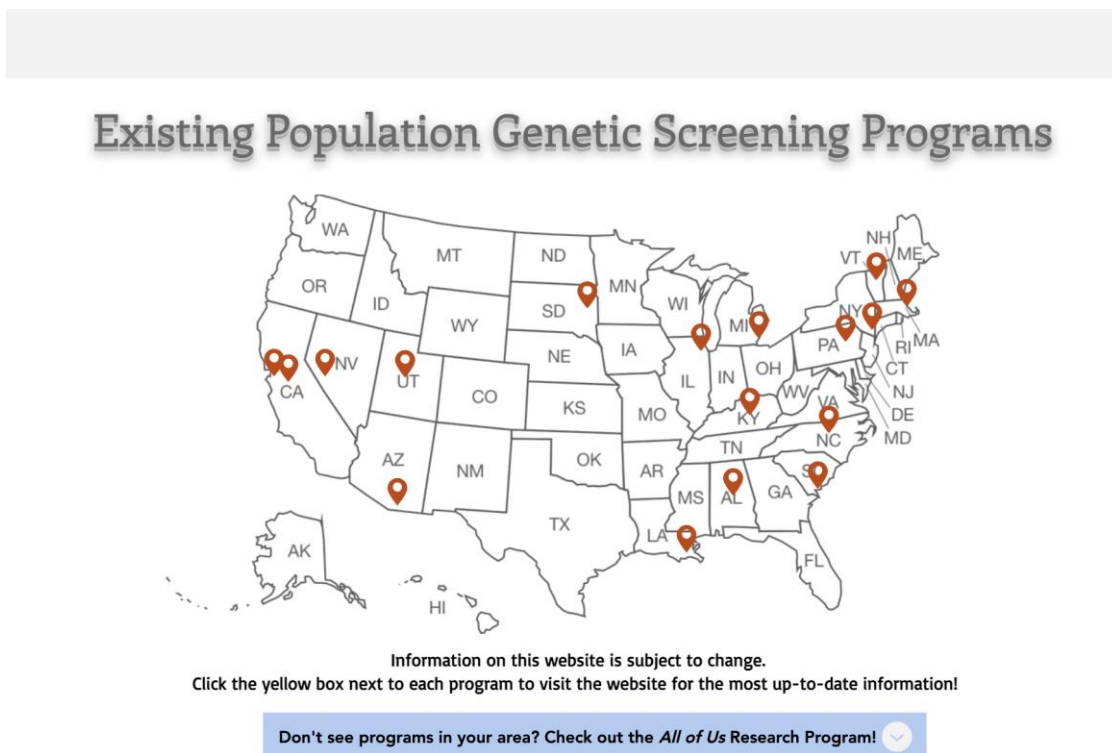
Finally, existing population screening programs are reviewed and mapped on a map of the United States (Figure 6). The location icons can be clicked to jump ahead to the program of interest. Each program has information about the conditions that it screens for and whether individuals will have an out-of-pocket cost. The yellow buttons with arrows next to each program can be clicked to visit their websites (Geisinger, n.d.; Healthcare, n.d.; Healthy NV Project, n.d.; Icahn School of Medicine at Mount Sinai, nd; Intermountain Healthcare, n.d.; Mass General Brigham, n.d.; Medical University of South Carolina MUSC, n.d.; NorthShore University HealthSystem, n.d.; Ochsner Health, n.d.; Precision Health University of Michigan, n.d.; Sanford Health, n.d.; Sciences, n.d.; The University of Vermont Medical Center, n.d.; UAB Medicine, n.d.; UCSF Health, n.d.-a, n.d.-b; UNC Health, n.d.). The readers can learn more about the programs and potentially contact them and/or enroll. Individuals who do not have nearby research programs can click on the blue box underneath the United States map to scroll down to the information about the *All of Us* Research Program.

This project identified 17 programs that provide opportunities for individuals to participate in a population genetic screening program. Initially, the list of programs began with 10 population screening programs obtained from Foss et al., which either have the active or unknown status of enrollment (Foss et al., 2022). These programs included Alabama Genomic Health Initiative (AL), Mass General Brigham Biobank (MA), Geisinger MyCode (PA), Healthy Nevada Project (NV), Ochsner Health innovationOchsner Population Genomic Screening Program (LA), the Sanford Chip (SD), St. Elizabeth Healthcare Precision Medicine and Genetics (KY), UCSF Preventative Genomics Clinic (CA), UCSF 3D Health (CA), and University of Vermont the Genomic DNA Test (VT). In addition to these 10 programs, 3 more programs were identified by the internet and

literature search – University of North Carolina (UNC) Health Precision Health Genetic Screen (NC), Medical University of South Carolina (MUSC) In Our DNA (SC), and Michigan Genomics Initiative (MI). All population genetic screening programs identified are research programs.

Some programs use CDC Tier 1 conditions and other programs use various versions of the ACMG SF list. Some other programs had their own panel that is influenced by these organizations. The details of two screening programs, Alabama Genomic Health Initiative (AGHI) and Mass General Brigham were updated with new information since Foss et al. (2022) was published – AGHI now screens for ACMG SF v3.0 instead of v2.0, and Mass General Brigham utilizes v2.0 instead of their own panel. Two programs were identified to have out-of-pocket costs by the participants: \$49 for the Sanford Chip and less than \$100 for the majority of the St. Elizabeth Healthcare program.

**Figure 6. Patient Education Resource – Existing Population Genetics Screening Programs**



**Alabama Genomic Health Initiative (AGHI), UAB Medicine, AL**

- Conditions/Genes tested: 73 actionable genes (ACMG SF v3.0)
- Costs: Free of charge to Alabama residents
  - Free of Charge Services include: testing, interpretation, and counseling

**Geisinger MyCode, Danville, PA**

- Conditions/Genes tested: 59 actionable genes (ACMG SF v2.0) + *HFE* gene
- Costs: Free of charge
- Expanded its service to southern New Jersey

**Healthy Nevada Project, Renown Health, NV**

- Conditions/Genes tested:
  - Three CDC Tier 1 conditions (HBOC, LS, & FH)
  - ancestry/traits
- Costs: Free of charge

**Icahn School of Medicine at Mount Sinai BioMe® BioBank Program, New York, NY**

- Conditions/Genes tested:
  - Three CDC Tier 1 conditions (HBOC, LS, & FH) + hereditary transthyretin amyloidosis (contact the institution for more information)
- Costs: Free of charge

**Intermountain Healthcare HerediGene: Population Study, Salt Lake City, UT**

- Conditions/Genes tested:
  - unclear (105 genes?) (contact the institution for more information)
- Costs: Free of charge
  - primarily serving intermountain's patient population from Utah and Idaho

**Mass General Brigham Biobank, Boston, MA**

- Conditions/Genes tested: 59 genes (ACMG SF v2.0)
- Costs: free of charge
- Other services may include (<https://www.brighamandwomens.org/medicine/genetics/genetics-and-genomic-medicine/preventive-genomics-clinic>)
  - Preventive genomic sequencing for healthy individuals
  - Genetic risk assessment for adopted individuals
  - Guidance for follow up on direct-to-consumer genetic testing results

**Medical University of South Carolina (MUSC) In Our DNA SC, Charleston, SC**

- Conditions/Genes tested:
  - Three CDC Tier 1 conditions (HBOC, LS, & FH)
  - ancestry/traits
- Costs: Free of charge

**Michigan Genomics Initiative, Ann Arbor, MI**

- Conditions/Genes tested:
  - 151 genes
  - ancestry
  - [pharmacogenetics](#), etc.
- Costs: Free of charge

**NorthShore University HealthSystem Genomic Health Initiative, Evanston, IL**

- Conditions/Genes tested:
  - 56 actionable genes (ACMG SF)
  - [pharmacogenetics](#)
- Costs: Free of charge



- Ochsner Health System innovationOchsner Population Genomic Screening Program, New Orleans, LA**
- Conditions/Genes tested: Three CDC Tier 1 conditions (HBOC, LS, & FH)
  - Costs: Free of charge
  - Unclear if still recruiting: the enrollment process is completely digital. Check out your patient portal or contact them.



**Sanford Health The Sanford Chip, Sioux Falls, SD**

- Conditions/Genes tested:
  - 57 genes (similar to ACMG SF v2.0)
  - [pharmacogenetics](#)
- Costs: self-pay (\$49)
- Genetic counselors are placed in primary care clinics in Sioux Falls, SD, Fargo, ND, Bismarck, ND, Bemidji, MN



**St. Elizabeth Healthcare Precision Medicine and Genetics, Edgewood, KY**

- Conditions/Genes tested
  - Invitae laboratory's proactive genetic panel:
    - cancer (61 genes)
    - cardiovascular diseases (75 genes)
    - [pharmacogenetics](#) (25 genes)
  - Genetic health panel: cancer & cardiovascular + additional conditions (147 genes)
- Costs: self-pay (over 90% of people spend <\$100; maximum out-of-pocket cost: \$250)
- Serving communities in n Kentucky, Ohio, and Indiana



**University of Arizona Health Sciences GenoBank, Tucson, AZ**

- Conditions/Genes tested:
  - 20-25 medically-relevant genetic traits (contact them to receive more information)
  - ancestry/traits
- Cost: Free of charge



**University of California at San Francisco (UCSF) Preventive Genomics Clinic, San Francisco, CA**

- Conditions/Genes tested:
  - 74 genes – cancer, cardiovascular disease, & pharmacogenetics
  - [carrier status](#)
- Costs: Free of charge



**University of California at San Francisco (UCSF) 3D Health, San Francisco, CA**

- Conditions/Genes tested:
  - 59 (ACMG SF v2.0)
  - ancestry/traits
  - [carrier status](#)
  - [pharmacogenetics](#)
- Costs: Free of charge



**University of North Carolina (UNC) Health Precision Health Genetic Screen, Chapel Hill, NC**

- Conditions/Genes tested:
  - Three CDC Tier 1 conditions (HBOC, LS, & FH)
- Costs: Free of charge for UNC Health patients



**University of Vermont The Genomic DNA Test, Burlington, VT**

- Conditions/Genes tested: 431 genes (including ACMG SF v2.0 & carrier status)
- Costs: Free of charge



Beyond screening for actionable genes, many programs offer testing for carrier status, ancestry/traits, and pharmacogenetics. Under each program, the website also includes whether the program screens for these traits. Hyperlinks attached to “carrier status” and “pharmacogenetics” helps explain what they are by referencing outside resources (ACOG, 2020; MedlinePlus, 2021). It is important that participants are well educated about the difference between being affected by an autosomal dominant condition under actionable genes versus being unaffected under carrier status screening. Participants should also be properly pre-consented and prepared to receive unexpected results, including their ancestral origin.

### **3.4.1 All of Us Research Program**

The last section of the Existing Population Genetic Screening Programs page has information about the *All of Us* Research Program (Figure 7). It briefly provides an overview of the project, what the program plans to screen for, and how to obtain more information/enroll in the program (NIH, 2022).

**Figure 7. Patient Education Resource – All of Us Research Program**

## All of Us Research Program

**All of Us Research Program** is a nationwide research program.  
Its goal is to enroll one million people of different backgrounds across the United States.  
It aims to speed up medical research in the future.  
It is part of the National Institute of Health (NIH) and is publicly funded.

[Learn More](#)

*All of Us* plans to screen for and return the result of 59 actionable genes assembled by ACMG. [1]

Listed below are the organizations that recruit people for the *All of Us* Research Program.  
Click the  icon to learn more and/or to sign up for the program!

Even if you do not have access to these Health Care Provider Organizations, you can still participate!

- ☐ Do you live in the United States?
- ☐ Are you 18 years or older?
- ☐ Can you give consent on your own?
- ☐ You are NOT in prison?

If you answered yes to all questions, you can enroll online. [2][3]

[Sign up page](#)

## All of Us Research Program Recruitment Sites



A total of 62 recruitment sites (HPOs) are mapped by the consortiums (All of Us Research Program, n.d.-a). The location icons and the U.S. Veterans Affairs icon will show the name of the

HPOs when the cursor is pointed at it. They can also be clicked to visit each consortium's website that provides more information about the program (All of Us Research Program, n.d.-a).

### **3.5 Patient-Friendly Resource Readability Assessment**

The average reading level of adults in the United States is at the 8<sup>th</sup>-grade level, and NIH and other organizations recommend that patient education materials be written at a 5-8<sup>th</sup> grade reading level (Eltorai et al., 2014; Stossel et al., 2012; Szabo et al., 2021). Using the Flesch–Kincaid readability tests, this website overall was determined to have a reading level of 8.2. Considering the complexity of genetics as its content, the website utilized visual aids and interactive features that would help facilitate the readers' understanding. Many sentences were kept shorter and in their active forms; 2.3% of the sentences on this website contained passive sentences.



## 4.0 Discussion

This project identified a total of 17 population genetic screening programs. These programs offer testing for three CDC Tier 1 conditions, ACMG SF list genes, or their own program's panel for actionable genes. As all of these programs are research projects, genetic testing is often provided to participants free of charge except for the Sanford Chip and St. Elizabeth Healthcare Precision Medicine and Genetics. The costs involved are \$49 for the Sanford Chip and less than \$100 for the majority of the St. Elizabeth Healthcare program, which can impact the accessibility of these services and potentially lead to exacerbating the health disparity in these communities. As discussed in Foss et al., measuring the impact of out-of-pocket cost on the uptake across different programs would be interesting to assess.

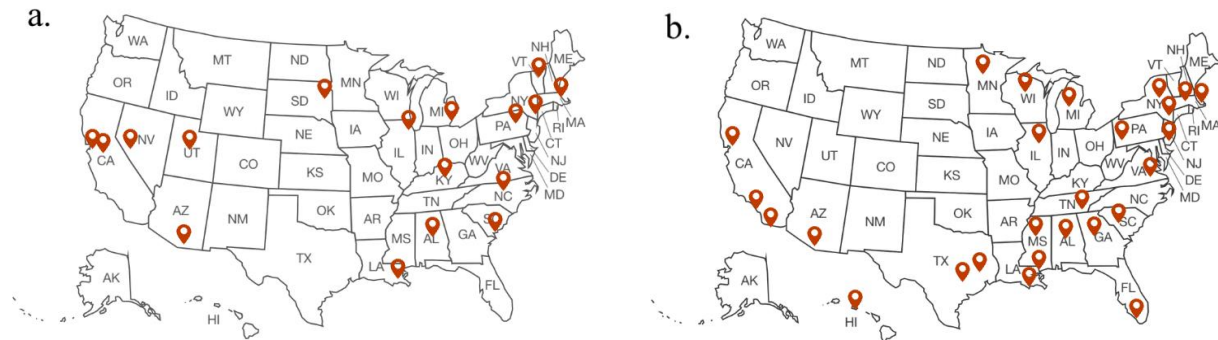
This essay project not only identifies the programs, but also mapped the existing population screening programs and the *All of Us* recruitment sites. This provided extra insight into existing screening programs.

### 4.1 Locations of Population Genetic Screening Programs and *All of Us* Research Program Recruitment Sites

After placing them on a map, it became apparent that many population genetic screening programs are clustered either in the western states or the eastern states, leaving a gap in the middle and northern west states. Interestingly, these independent population screening programs are distributed similarly to 62 recruitment sites of the *All of Us* Research Program (Figure 8). This can

potentially be due to having stakeholders and/or public health professionals who advocate for population screening programs in these areas.

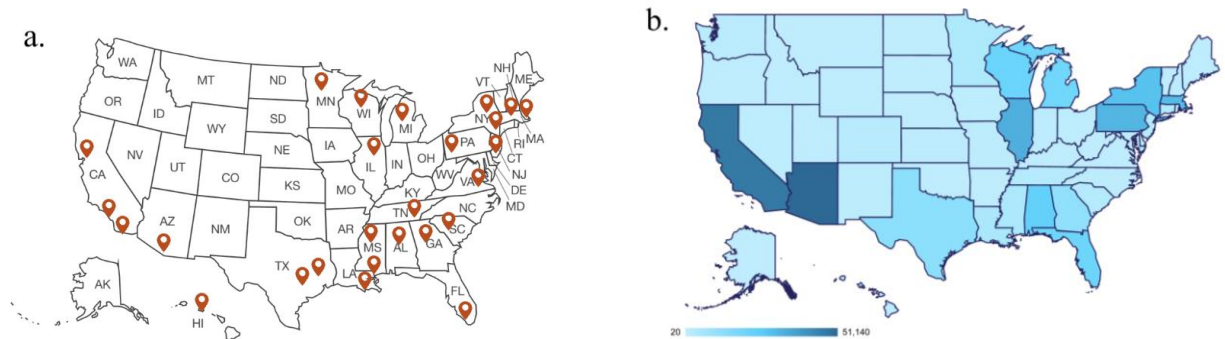
**Figure 8. Comparison of Population Genetic Screening Programs vs. *All of Us* Recruitment Sites**



The maps represent the locations of (a) existing population genetic screening programs and (b) the recruitment sites for the *All of Us* Research Program.

Furthermore, the number of *All of Us* participants are seemingly aligned with the availability of enrollment sites (Figure 9) (All of Us Research Program, 2022). As HPOs make efforts in bringing individuals, families, and communities into the *All of Us* by answering questions and guiding them through the enrollment process, the presence of enrollment sites could significantly influence the number of participants. This may speak to the importance of expanding enrollment sites by partnering with the medical centers in the areas that are yet to have HPOs for the *All of Us* Project in order to truly create a study sample reflective of the United States.

**Figure 9. Comparison of All of Us Recruitment Sites and the Number of Participants in Each State**



The maps represent (a) the recruitment sites for the *All of Us* Research Program and (b) the number of *All of Us* participants in each state obtained from their website: <https://www.researchallofus.org/data-tools/data-snapshots/>. The number of participants increases as the blue color is darker.

In addition to the location of enrollment sites, other factors such as demographics, political beliefs, or ethnic and cultural background may also affect an individual's interest in research projects like *All of Us*.

Having the HPOs partner with the *All of Us* may be the first step in facilitating the conversation between local communities and the research program, which may help alleviate the disparity. Similarly, more efforts in identifying potential explanations and expansion of HPOs should be made in order to reduce the health disparity in areas where low participant rates to *All of Us* exist and local population genetic screening programs are not available.

## 4.2 Limitations and Future Directions

This project had a number of limitations. Individual local population genetic screening programs were searched online using state names and other key terms, such as population screening, actionable genes, and biobank. The programs that were identified can be hugely

influenced by the search terms used and the hits on the Google search engine. Moreover, some population genetic programs and/or biobanks do not have detailed information publicly available on their web page. These programs could have plans to return actionable gene lists, yet such information would not be apparent unless the organization would be contacted. More studies like this should be conducted to gather additional information on programs. Public health stakeholders should create public resources that can address these issues. Although details of each program's consent and return of result processes or the purpose of this essay, future studies should investigate this information and make it readily accessible to the general public to further facilitate their participation and understanding.

## 5.0 Conclusion

To date, no database or central reporting system that keeps track of existing population genetic screening programs exists. Only one paper, which was recently published, made an effort in identifying existing programs using online resources and scientific literature searches. A similar approach was taken during this project, and additional programs were identified. Even CDC's State Public Health Genomics Program Map is not up to date or comprehensive— only Alabama Genomic Health Initiative (AL) and Healthy Nevada Project (NV) are on their list – although the majority of states they covered had newborn screening programs and cancer screening program information. When searching for population genetic screening programs, it became apparent that many states are not focusing on these types of initiatives, thus identifying individuals with genetic conditions among high-risk populations remains the most common model of testing. While it is still important to follow testing criteria to recognize these individuals, some conditions have emerging evidence to support screening in the general population. While many institutions and public health organizations put effort into making this shift from high-risk populations to general population genetic screening, patient-friendly tools to identify programs were limited. Linking people to appropriate health services is one of the important assets of the 10 essential components of public health as part of assurance.

In an emerging era of population genetic screening, the creation of a national and/or state database that is accessible to providers and lay individuals about existing programs and their information may be an essential next step. Such a resource is not only essential to facilitate individuals to make their own health decisions, but also important to help bridge similar programs

to fill the knowledge gaps that still exist about the clinical utility and validity of population screening before it can be expanded beyond research applications.

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