The Genomic Medicine for Everyone (Geno4ME) Study: Implementation of Whole Genome Sequencing for Population Screening in a Large Healthcare System

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Abstract

Population-scale genomics programs may enable increased access to genomic medicine. The Genomic Medicine for Everyone (Geno4ME) program was established across the diverse seven-state Providence Health system to enable genomics research and genome-guided care pathways across patients' lifetimes. Key components included targeted and multi-lingual outreach to underrepresented groups, a novel electronic informed consent (e-consent) and education platform, and whole genome sequencing (WGS) with clinical return of results and integration into the electronic health record (EHR) for 78 hereditary disease genes and four pharmacogenes. Clinical whole genome sequences were banked for research, programmatic expansion of returnable results, and variant reanalysis. The program provided genetic counseling, pharmacist support, and guideline-based clinical recommendations for patients and their providers. During the two years of the study, over 30,800 potential participants were contacted; out of these, 2,716 were consented to the study (of which 47.5% were people of color) and 2,017 had results returned. One hundred fifty-eight (7.8%) participants had an actionable gene variant in the hereditary disease panel, 294 (14.6%) of participants had a pharmacogenomic (PGx) recommendation for one or more of the supported medications reported at time of enrollment, and overall, 21.4% of participants had a test result with at least one medical intervention recommendation. Future work will involve strategies to maintain engagement and education around genomic medicine. We propose the Geno4ME model as a framework to integrate population health genomics into routine healthcare and present lessons learned that may aid in the design of future programs.

Introduction

Genetic factors contribute to risk for most of the common medical health conditions affecting the U.S. adult population today, including heart disease, diabetes, cancer, and neurodegenerative diseases.[1–4] In addition to the cumulative impact of common, low-impact genetic variants in these chronic conditions, large-scale sequencing projects have elucidated the frequency of less common but highly clinically impactful genetic variants such as those defined by the American College of Medical Genetics & Genomics (ACMG).[5] These rare high-impact variants result in increased risk for inherited cancers, cardiomyopathies, and other conditions. While some individuals are aware that they have an increased risk of disease because of their family history, many others are unaware and unlikely to receive genetic/genomic testing prior to disease presentation.[6–8] For example, one recent study found that over 90% of individuals who had a pathogenic/likely pathogenic (P/LP) genetic variant in one of the genes associated with increased risk for BRCA-associated hereditary breast and ovarian cancer, Lynch syndrome, or familial hypercholesterolemia were previously undetected.[8] Furthermore, only 25% of these individuals with reported increased genetic risk had a known family history of the relevant disease, and another study found that 43% of participants who harbored P/LP variants did not meet guideline-based criteria for genetic testing.[9] In addition, in a national analysis from less than ten years ago, among individuals with a history of cancer who met the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for testing, only 1 in 5 reported being offered genetic testing.[10]

Results such as these suggest that proactive population genetic screening could be an avenue to improve the identification of individuals who have increased genetic risk for disease. Genetic screening of populations to identify at-risk patients could have large impacts on early disease detection, prevention, and healthcare costs, but is still not a widely established clinical practice; population screening has largely remained in the realm of large-scale research sequencing programs. While population screening programs have been demonstrated to be cost-effective for at least CDC Tier 1 conditions, these models rely on high-prevalence, high-penetrance conditions in populations that traditionally have high healthcare utilization. It remains to be seen if these models bear out in more diverse communities and/or when screening for additional genetic conditions. [8,11]

Genetic factors can also contribute to inter-individual differences in drug metabolism and responses. Pharmacogenomic (PGx) variants can influence the treatment outcomes related to drug efficacy and risk of adverse drug reactions (ADRs). In a large study, 99% of the 7.7 million US veterans using the Veteran Health Administration were projected to have at least one actionable genetic result as defined by published Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. [12] PGx testing has demonstrated potential promise in reducing the risk of ADRs for the treatment of many health conditions, including cardiovascular disease, depression, gastroesophageal reflux disease, cancer, and pain.[13] While it has been shown that PGx-guided prescribing can improve medication safety, shorten trial-and-error periods, and increase therapy adherence to achieve optimal clinical outcomes, the adoption remains low.[14]

Current bottlenecks that limit the utilization of inherited disease and PGx genetic information in patient care include lack of tools for integration with electronic health record (EHR) systems, provider and patient familiarity with genomic medicine and cost and comprehensiveness of current clinical genetic assays. Additionally, population genetic screening could help in closing the large gaps in disease outcomes related to race/ethnicity, socioeconomic status, and other social determinants of health. [15,16]

A key challenge with population genetic screening is the limited genomic content in current screening panels especially given the rapid expansion of the number of known actionable gene targets, as well as the introduction of genome-scale risk biomarkers such as polygenic risk scores (PRS). However, given rapid advances in next generation sequencing (NGS) technology resulting in higher throughput and low-cost whole genomes, a preeminent strategy is to perform one-time complete whole genome sequencing (WGS) for all patients that can be continually reanalyzed thus eliminating the potential need for resequencing with additional panels as new genomic indications become available. Technological innovations of the last five years such as EHR-embedded clinical decision support (CDS), AI-enabled tertiary analysis of sequencing data, and markedly decreasing costs of WGS provide healthcare systems the unique opportunity to offer precision health using WGS. Integration of WGS data with clinical and self-reported risk factors such as family history, health behaviors, and social determinants of health data could allow for the detection of known genetic risk factors that can be reported to patients and their health care providers for appropriate clinical monitoring and intervention. Additionally, when used for research, the integrated genomic, clinical, behavioral, and social determinants data can fuel the discovery of new genetic markers and increase our understanding of their contributions to clinical disease.

While some health systems have effectively launched strategies that leverage intensive provider engagement in recruiting patients for genomic screening, these approaches may not be scalable in large, diverse, multi-state health systems with decentralized management structures or a high percentage of providers that are contracted or not directly employed by the health system. Additionally, national biorepository efforts such as the NIH All of Us Research program operate largely outside a patient's clinical care team and lack a direct pathway to downstream care.

Providence is one of the largest community health systems in the United States, with more than 50 hospitals and 1,000 clinics across seven states, and over 30,000 providers. In our Providence health system, we designed and executed a scalable clinical implementation study, "Genomic Medicine for Everyone" (Geno4ME), using clinical WGS to screen individuals for high-impact clinical variants that can change patients care experience – more specifically, we focused on genetic variants related to cancer, cardiovascular disease, and other medical conditions, as well as variants related to PGx. We screened for genes or variants that have a well-established association with disease risk or PGx and where knowledge of the pathogenic variant warrants medical recommendations based on published guidelines. For example, participants with genetic variants related to increased cancer risk were advised according to the established NCCN Guidelines on appropriate screenings for early detection and preventive plans to decrease the risk of developing cancer.[17,18] Similarly, specific guideline-based clinical recommendations were provided for participants with pathogenic or likely pathogenic variants in any of the 59 genes determined to be clinically actionable and reportable by the ACMG for secondary findings in clinical exome and genome sequencing.[5] To supplement the genetic data and create a more complete picture of healthcare-related risks and needs, there is ongoing longitudinal data collection on clinical measures from the EHR and self-reported survey responses. Here we report results from the initial phase of the study as well as insights gained that may inform the future design of genome-enabled healthcare.

Methods

Participant Eligibility

This study was reviewed and approved by the Providence Health Institutional Review Board (approval number STUDY2020000637). To be eligible, participants had to be over the age of 18 and a current patient within the Providence system with a minimum of one visit with a provider in the Providence network within the previous 12 months. Participants must have been willing to provide the name and contact information for their primary Providence provider who would receive the lab report. All racial and ethnic backgrounds were eligible; however, due to limitations in participant educational and consent materials, enrollment at initial program launch was restricted to participants who understood English or Spanish and could enroll electronically. As consenting took place remotely, participants had to have a viable email address, current address to receive mail, and telephone number. Participants were excluded if they were under 18 years old, pregnant, had a history of bone marrow transplantation, or had an active hematologic malignancy.

Participant Outreach and Recruitment

Figure 1 describes the overall participant journey starting with the point of initial outreach/invitation. Between March 2021 and April 2023, eligible Providence patients were invited to participate in Geno4ME. Participants were able to return their sample kits until June 30, 2023. Invitation occurred in two phases: the first phase from March-September 2021 was a clinic-centered outreach approach for purposes of assay and process validation that involved recruitment through three participating clinics located in Oregon (OR), California (CA), and Washington (WA) (i.e. clinic-based outreach), and the second phase from September 2021 onward involved direct-to-patient, population-level outreach using stratified random sampling of diverse populations in five states (Oregon, California, Washington, Alaska (AK), and Montana (MT)) within the Providence system (i.e. population outreach). Outreach initially began in California and Oregon in September 2021 given the enrichment of patients meeting sampling criteria in these locales and was expanded to include Washington, Montana, and Alaska in May 2022.

Clinic-based recruitment involved identification of patients with an upcoming appointment at that clinic and MyChart provided to the patient by a research coordinator and/or clinic staff two weeks prior their scheduled appointment or a flyer invitation during their visit. To increase participation by patients who are underrepresented in genomic studies to date, we used population-level stratified random sampling focused on outreach to patients of Asian, Black, and Hispanic ancestry, patients whose first language was Spanish, and patients whose primary insurance was Medicaid (as a proxy for socioeconomic status and healthcare vulnerability). Recruitment outreach involved combinations of mail, email, text messages, and autocalls in two languages (English and Spanish).[19]

Enrollment Process

Participants could enroll in Geno4ME online using a novel e-consent platform designed and built by our health system that included hosting of the study website, with information about the genetic test and frequently asked questions (FAQ) guides, and a step-by-step consent process with pre-enrollment educational materials with videos (Fig. 1). Other than for COVID, this was the first complete e-consent process approved in our health system. Individuals interested in joining Geno4ME were asked to create a study account to access the e-consent platform and sign consent documents. Participants were able to select their preferred language, English or Spanish, on the study website and e-consent platform. Study accounts were also used for participants to answer surveys in a private and secure manner, access their genetic report, consent document, and some post-enrollment education, as well as change their opt-in status regarding future research study opportunities.

As part of the enrollment process, participants were asked to answer a brief questionnaire about their personal and family medical history, which was used during the report generation process and future interpretation of results. It included questions on race and ethnicity, self-reported personal and family history of cancer and cardiovascular disease, and current use of one of the 7 medications included in the PGx part of the genetic screen. Self-reported personal and family history questions collected at enrollment were based on National Comprehensive Cancer Network (NCCN) Guidelines (for cancer) and Heart Rhythm Society (HRS) and European Heart Rhythm Association (EHRA) consensus statements (for cardiovascular disease) to assess whether patients would meet

the threshold for detailed risk assessment and genetic counseling. Additionally, to understand better how genetic, clinical, and social risk factors influence the trajectory of health and disease, time-specific surveys were sent via the electronic platform immediately after enrollment, at 12 months after receipt of results, and at 24 months after receipt of results (12- and 24-month follow-up surveys are still ongoing). These surveys included questions about health behaviors, social determinants of health, and access to care. The purpose of the surveys was twofold: first, surveys were used by the laboratory for generation of the tailored clinical report, and second, the de-identified data from longitudinal surveys will be incorporated into the Geno4ME biorepository to enable research into intersectional risks between genetic, clinical, family history, health behavior, and social risk factors in the participating populations.

Sample Collection

The collection sample was divided into two phases; phase 1, which involved both blood and saliva sample collection was limited in number of participants and solely designed for the validation of our WGS assay and process. The following phase 2 sample collection, only mailed saliva collection kits were used, was designed to be more scalable, easier for participants, and easier for clinic staff and mirror a true population-based approach. Ultimately, 88.7% of all study participants were part of phase 2.

Phase 1 Sample Collection – Clinic-Based

To validate our Geno4ME assay and processes, phase 1 of sample collection involved collection by local staff at a patient appointment/encounter. Participants were asked to provide two samples (blood and saliva) at a local clinical encounter. For the blood sample collection, a licensed phlebotomist at the clinic or a Providence laboratory patient service center collected 8-10mL whole blood in standard clinical use EDTA tubes and 5 mL in standard clinical use PPT Pearl tubes; for the saliva sample collection, a research coordinator assisted the patient to collect the saliva sample (2 mL) using an Oragene Saliva DNA Collection kit (DNA Genotek). Each saliva kit and blood collection tube was labeled with a participant's identifying information before it was distributed, as required by Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) regulations. Each specimen was transferred via courier (within Oregon) or FedEx overnight shipping at room temperature to the Providence Molecular Genomics Laboratory (MGL; Portland, Oregon, CLIA # 38D2032720, CAP # 8034828). In September 2021, following phase 1 assay and process validation, all enrollment channels, including the clinic-based cohort, were transitioned to the phase 2 saliva-based population outreach sample collection workflow described below.

Phase 2 Sample Collection – Population Outreach

In the second phase, upon enrollment participants were provided an Oragene Saliva DNA Collection kit (DNA Genotek) that was mailed directly to their residence. Our study platform automatically sent a kit fulfillment request once the patient was consented that resulted in the kit being sent to the patient. Each kit was labeled with a participant's identifying information before it was distributed. For the saliva sample collection, participants provided their sample (2 mL) at home using the instructions provided. Once the saliva sample was collected, participants mailed the sample at room temperature using approved regulatory and postage prepaid packaging to the study laboratory, the Providence MGL. If the participant's primary saliva sample failed, they were offered the option to provide a blood sample at a Providence phlebotomy station. For the blood sample collection, a phlebotomist collected 8-10mL whole blood in standard clinical use EDTA tubes which were transferred via courier (within Oregon) or FedEx overnight shipping at room temperature to the Providence MGL.

WGS-based Assay Workflow and Validation Process

DNA extraction from blood and/or saliva was performed using the QIAsymphony DSP Midi Kit on a QIAsymphony instrument (Qiagen). WGS libraries were prepared from 300 to 500 ng gDNA with the Illumina DNA PCR- Free Prep, Tagmentation kit and was sequenced on an Illumina Novaseq 6000. Genomic secondary analysis for the genes included in the Geno4ME test was performed using standard analysis pipelines on the Illumina DRAGEN (Dynamic Read Analysis for GENomics) Bio-IT Platform.

A validation set of 188 (119 whole blood and 69 saliva, with 60 paired/blood saliva specimens) DNA samples from newly enrolled patients as well as known positives and control reference materials were used to validate the assay along with orthogonal testing at a CLIA/CAP commercial molecular laboratory (Invitae). A training set of 18 DNA samples from the CDC Genetic Testing Reference Material program (GeT-RM) was used in addition to the blood/saliva DNA patient samples for the validation of the PGx results. [20] These 18 samples were sequenced at MGL following the same procedure as the DNA samples from the study participants.

Variant Curation and Confirmation

An initial variant prioritization and scoring was performed using the Health Insurance Portability and Accountability Act (HIPAA)-compliant Fabric Genomics cloud platform.[21] For PGx, pre-selected variants were genotyped and phenotypes were assigned in the Fabric Genomics platform based on PharmGKB, Clinical Pharmacogenetics Implementation Consortium (CPIC), and Pharmacogene Variation Consortium (PharmVar) annotations. [22–24] For inherited diseases, variants were automatically annotated and classified using the Automated Variant Classification Engine (ACE) from Fabric Genomics. ACE is a scoring module based on the 2015 guidelines for variant interpretation from ACMG and the Association for Molecular Pathology (AMP),[25] which utilizes evidence from public databases, such as ClinVar, dbSNP, and gnomAD, to classify and prioritize variants. The curation and final classification assignment of the variants of interest identified by ACE (i.e., P/LP variants, certain prioritized variants of unknown significance (VUS), as well as structural variants) were completed in-house by Clinical Scientists using the 2015 ACMG guidelines and Mastermind literature search engine.[25,26] Variants were either classified as P/LP and included in the clinical report or as VUS, which were not returned to the participants. After this final review, the presence of P/LP variants associated with inherited disease(s) was independently confirmed by an independent third-party laboratory, Invitae, using an industry-standard orthogonal NGS process (Fig. 1).

Geno4ME Return of Results Panel Design

As part of the enrollment in the Geno4ME study, clinically actionable genetic results were reported back to participants and providers to guide clinical decisions for preventive health or disease management. Consenting to the study required consenting to return of results; the participants were not able to "opt out". While WGS was performed, the data analyzed for the return of results was limited to the genes selected for assessing inherited disease risk and pharmacogenomics. All other regions of the genome outside the scope of the Geno4ME return of results were bioinformatically masked for the team preparing the clinical interpretation and report. For inherited diseases, the gene panel included clinically relevant genes that have a well-established association with disease risk, especially cancer and cardiovascular disease, and where knowledge of the pathogenic variant warrants medical recommendation based on published guidelines. The panel included the 59 genes identified by the ACMG as relevant secondary findings to return from sequencing (ACMG 59)[5] and 18 additional genes with actionable management recommendations by the 2021 NCCN Guidelines for genetic/familial cancer risk (Table 1).[27,28] For PGx, the panel included 7 gene-drug pairs that were selected based on FDA and CPIC guidelines as well as prescription usage data across the Providence St. Joseph Health (PSJH) system and races/ethnicities (Table 2; FDA, Table of Pharmacogenomic Biomarkers in Drug Labeling).[29–31] PGx variants were pre-selected based on the published joint recommendations from the AMP and the CAP, as well as CPIC guidelines. For *CYP2C19*, both Tier 1 (*2, *3, and *17) and Tier 2 (*4A, *4B, *5, *6, *7, *9, *10, and *35) alleles were included per AMP/CAP recommendation.[32] As recommended by the CPIC guideline for warfarin, *CYP2C9* Tier 1 alleles (*2, *3, *5, *6, *8, and *11), *VKORC1* (c.-1639G > A, rs9923231), *CYP4F2* (*3), and the single variant rs12777823 (*CYP2C* cluster) were initially included. [33,34] For the variant analysis, a 5,000 bp buffer region on both sides of each gene of both panels was included. For three genes, *GREM1, EPCAM*, and *PMS2*, the analyzed regions were expanded farther out to include large known duplications and deletions.[35]

Table 1
List of genes, associated diseases included in the inherited disease panel

Gene	Disease(s)	Disease category
APC	Familial adenomatous polyposis	Cancer
ATM	Ataxia-telangiectasia (includes ATM-related cancers)	
AXIN2	Oligodontia-colorectal cancer syndrome	
BMPR1A	Juvenile polyposis	
BRCA1	Hereditary breast and ovarian cancer	
BRCA2		
BRIP1	BRIP1-related cancers	
CDH1	Hereditary diffuse gastric cancer syndrome	
CDK4	Hereditary cutaneous melanoma	
CDKN2A	Hereditary melanoma-pancreatic cancer syndrome	
CHEK2	CHEK2-related cancers including breast, colon and other sites	
EPCAM	Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome)	
MLH1		
MSH2		
MSH6		
PMS2		
GREM1	Hereditary mixed polyposis syndrome	
MEN1	Multiple endocrine neoplasia type 1	
MLH1	Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome)	
MSH2		
MSH3	MSH3-associated polyposis	
MUTYH	MYH-associated polyposis; adenomas, multiple colorectal, FAP type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	
NBN	NBN-related cancers	
NF1	Neurofibromatosis type 1	
NF2	Neurofibromatosis type 2	
NTHL1	NTHL1-associated polyposis	
PALB2	PALB2-related cancers	
POLD1	POLD1-related cancers	
POLE	POLE-related cancers	
PTEN	PTEN hamartoma tumor syndrome	
RAD51C	RAD51C-related cancers	
RAD51D	RAD51D-related cancers	
RB1	Retinoblastoma	
RET	Multiple endocrine neoplasia type 2	
RET	Familial medullary thyroid cancer	
SDHAF2	Hereditary paraganglioma pheochromocytoma syndrome	
SDHB		
SDHC		
SDHD		
SMAD4	Juvenile polyposis and Hereditary hemorrhagic telangiectasia	
STK11	Peutz-Jeghers syndrome	

Gene	Disease(s)	Disease category
TP53	Li-Fraumeni syndrome	
TSC1	Tuberous sclerosis complex	
TSC2		
VHL	Von Hippel-Lindau syndrome	
WT1	WT1-related Wilms tumor	
LDLR	Familial hypercholesterolemia	Hyperlipidemia
PCSK9		
APOB	Familial hypercholesterolemia and Familial hypobetalipoproteinemia	
DSC2	Arrhythmogenic right ventricular cardiomyopathy	Cardiomyopathy
DSG2		
DSP		
PKP2		
TMEM43		
ACTC1	Hypertrophic cardiomyopathy, dilated cardiomyopathy	
GLA		
LMNA		
MYBPC3		
MYH7		
MYL2		
MYL3		
PRKAG2		
TNNI3		
TNNT2		
TPM1		
SCN5A	Brugada syndrome	Arrhythmia
RYR2	Catecholaminergic polymorphic ventricular tachycardia	
SCN5A	Romano-Ward long-QT syndrome types 1, 2, and 3	
KCNH2		
KCNQ1		
COL3A1	Ehlers-Danlos syndrome, vascular type	Aneurysm/
ACTA2	Familial thoracic aortic aneurysms and dissections (FTAAD)	Connective tissue
MYH11		
SMAD3	Loeys-Dietz syndrome	
TGFBR1		
TGFBR2		
FBN1	Marfan syndrome	
TGFBR1		
CACNA1S	Malignant hyperthermia susceptibility	Other
RYR1		
OTC	Ornithine transcarbamylase deficiency	
ATP7B	Wilson disease	

Table 2
List of the seven gene-drug pairs included in the pharmacogenomics panel.

Drug class	Drug name	Gene/rsID
Antidepressants (SSRIs)[a]	Celexa® (citalopram)	*CYP2C19*
	Lexapro® (escitalopram)	
Proton pump inhibitors (PPIs)	Prevacid® (lansoprazole)	*CYP2C19*
	Prilosec® (omeprazole)	
	Protonix® (pantoprazole)	
Anticoagulants/Antiplatelet agents	Plavix® (clopidogrel)	*CYP2C19*
	Coumadin® (warfarin)	*VKORC1*
		CYP2C9
		CYP4F2
		rs12777823 (*CYP2C* cluster)

[a] Selective serotonin reuptake inhibitors (SSRIs)

Return of Results Process to Patient and Provider

Results were delivered electronically to the participants and the provider they indicated during the enrollment process, as well to genetic counselors when appropriate (Fig. 1). Positive results for the inherited disease panel were defined by the presence of one or more P/LP variant(s) in any of the 77 genes. The associated condition was reported alongside the variant identified; of note we reported the I1307K variant within the *APC* gene as associated with "colorectal cancer" only. VUS were not reported for the inherited disease panel given the screening nature of the program.

The genetic results report included a cover letter to providers that explained: 1) the purpose of the study, 2) if one or more P/LP variant(s) had been identified, 3) whether the patient had reported a personal and/or family history of specific cancer and cardiovascular conditions that may be associated with inherited risk for disease and warrant further referral to genetic counseling (based on answers to the enrollment survey). The result report also included links to a Geno4ME provider portal for clinical support educational material in the form of 1–2 page, gene-specific "Just In Time" information sheets -- which summarized clinical risks, condition management recommendations, and next steps for the participant, created, updated, and hosted by study partner and telehealth genetic counseling provider Genome Medical (GM). For patients seen by a GM genetic counselor (as described below), providers were sent the participant's personalized guideline-based action plan generated from GM their genetic counseling appointment.

Participants with a positive result for the inherited disease panel were contacted by a PSJH research coordinator by phone and/or email to initially disclose the results and arrange a genetic counseling consultation appointment through Genome Medical, for individualized care recommendations. After completion of a genetic counseling visit, the patient and their provider were given a personalized care plan developed by the GM genetic counselor. If the participant did not reply after 6 outreach attempts (phone and/or email), results were provided automatically through MyChart and their Geno4ME participant portal. The patient was given resources if they wished to schedule genetic counseling for a personalized care plan in the future.

Participants who had a clinically actionable PGx genotype/phenotype for a drug that they reported taking at time of enrollment were offered a PGx consultation with a pharmacist. When warranted, following the PGx consultation, a medication action plan was then shared with their provider for any alterations to prescriptions. The Geno4ME provider portal also included clinical decision support material for the 7 gene-drug pairs.

Research Data Management and Biorepository

In addition to the clinical report returned by Geno4ME, participants consented to the storage and approved researchers' use of de-identified data in aggregate to support research into risk factors for disease and evaluate intersectional risks between genetic, clinical, family history, health behavior, and social risk factors in the participating populations. Upon enrollment, each participant was assigned a unique Subject ID Number by Providence's self-built, HIPAA-compliant, cloud-based platform for patient education, engagement, and consent. Geno4ME resources (processed WGS data including binary alignment map (BAM) and variant call format (VCF) files, survey responses, and clinical EHR extracts) were de-identified, tagged with the MPT-generated Subject ID Number, and stored in a password-protected and encrypted cloud-based infrastructure.

Statistical Analysis

Chi-square tests of independence were performed to assess associations between categorical variables. Where race/ethnicity was analyzed as a variable, the "other" race/ethnicity category was excluded because of too few instances.

Results

Enrollment and Demographics

Over the course of the study enrollment period (from March 2021 to April 2023), potential participants across seven states received direct outreach (N = 27,787) or were invited through participating clinics (N = 3,091) (Tables 3 and 4). At the end of the sample return period (June 2023), 2,716 had been

consented to the study (8.8% overall enrollment uptake rate). Overall, 70.6% of the cohort reported as assigned female at birth, and 47.5% self-identify as racial or ethnic minorities: 14.3% Hispanic, 14.2% Asian, 8.2% more than one race, 8.1% Black, 2.7% other (Table 5). The participants' ages spanned a wide range from 18 to 96 (average 51.3 ± 15.3). When compared to the clinic-based outreach approach, the individuals consented through the population outreach approach were of more diverse race/ethnic background (57.2% vs 9.2% racial or ethnic minorities), younger (39.5% vs 23.9% ≤ 45 years old), and more likely to report as male at birth (30.7% vs 20.6%). The clinic sample was not sampled for diversity recruitment and was reflective of the local population/ disease centered clinic. Of the 2,716 participants who consented, 2,092 (77.0%) provided at least one blood and/or saliva sample and 2,017 (74.3%) had sequencing completed and received a report with clinical results. Reasons for consented participants not receiving a clinical result report included: participant never provided a sample for sequencing, participant provided a sample that resulted in technical sample failure, participant never provided a. Of the consented patients who did not receive results (n = 699), 624 never sent an initial sample for sequencing and 75 sent samples that ultimately resulted in sequencing failure (quality or quantity of DNA not sufficient, or QNS, for WGS). Of these 75 QNS, 22 were true technical failures who submitted multiple samples (21 participants submitted 2 samples and 1 participant submitted 3 samples) and 53 were initial technical failures who did not return a second sample for sequencing.

Table 3
Number of contacted individuals who are actively consented or withdrew

	Contacted N = 30,878	**Active consented N = 2,716**	**Withdrawn N = 32**	**Uptake rate**
Outreached	27,787	2,123 (78.2%)	25 (83%)	7.6%
Clinic invitation	3,091	476 (17.5%)	2 (7%)	15.4%
Other/Self-referred	NA	117(4.3%)	5 (17%)	NA

Table 4
State distribution of Geno4Me participants (overall and for clinic invitation enrollment channel)

	Overall		**Clinic invitation**	
State	N	Percent	N	Percent
CA	1,186	43.7%	77	16.2%
OR	995	36.6%	251	52.7%
WA	398	14.7%	146	30.7%
MT	71	2.6%	0	0%
AK	52	1.9%	0	0%
Other	14	0.5%	2	0.4%
Total	2716	100%	476	100%

Table 5
Demographic characteristics of individuals who enrolled in Geno4ME, provided a DNA sample, and received a clinical report when looking at the overall, t
outreached, and the invited through participating clinics populations.

	Enrolled			Provided at least one sample				Received a clinical report[d]			
	Overall N = 2,716	Outreached N = 2,123	Clinics N = 476[a]	Overall N = 2,092	Outreached N = 1,611	Clinics – Phase 1[b] N = 236	Clinics – Phase 2[c] N = 145	Overall N = 2,017	Outreached N = 1,539	Clinics – Phase 1 N = 236	Cli Ph N =
Race/Ethnicity											
Asian	385 (14.2%)	370 (17.4%)	6 (1.3%)	293 (14.0%)	281 (17.5%)	4 (1.7%)	2 (1.4%)	275 (13.6%)	264 (17.2%)	6 (1.6%)	2 (
Black	221 (8.1%)	214 (10.1%)	3 (0.6%)	167 (8.0%)	161 (10.0%)	1 (0.4%)	1 (0.7%)	157 (7.8%)	151 (9.8%)	2 (0.5%)	1 (
Hispanic	389 (14.3%)	365 (17.2%)	16 (3.4%)	268 (12.8%)	251 (15.6%)	4 (1.7%)	6 (4.1%)	259 (12.8%)	242 (15.7%)	10 (2.6%)	6 (
White	1,426 (52.5%)	908 (42.8%)	432 (90.8%)	1,148 (54.9%)	722 (44.8%)	217 (91.9%)	134 (92.4%)	1,122 (55.6%)	698 (45.4%)	351 (92.1%)	13 (92
More than one	222 (8.2%)	202 (9.5%)	15 (3.2%)	162 (7.7%)	149 (9.2%)	7 (3.0%)	2 (1.4%)	153 (7.6%)	140 (9.1%)	9 (2.4%)	2 (
Other	73 (2.7%)	64 (3.0%)	4 (0.8%)	54 (2.6%)	47 (2.9%)	3 (1.3%)	0 (0.0%)	51 (2.5%)	44 (2.9%)	3 (0.8%)	0 (
Sex at birth											
Female	1,924 (70.8%)	1,471 (69.3%)	378 (79.4%)	1,475 (70.5%)	1,109 (68.9%)	197 (83.5%)	105 (72.4%)	583 (28.9%)	1,069 (69.5%)	197 (83.5%)	10 (72
Male	792 (29.2%)	652 (30.7%)	98 (20.6%)	617 (29.5%)	502 (31.1%)	39 (16.5%)	40 (27.6%)	1434 (71.1%)	470 (30.5%)	39 (16.5%)	40 (27
Age group											
18–35	497 (18.3%)	442 (20.8%)	43 (9.0%)	331 (15.8%)	292 (18.1%)	20 (8.5%)	9 (6.2%)	318 (15.8%)	279 (18.1%)	20 (8.5%)	9 (
36–45	485 (17.9%)	397 (18.7%)	71 (14.9%)	337 (16.1%)	270 (16.8%)	31 (13.1%)	22 (15.2%)	324 (16.1%)	258 (16.8%)	31 (13.1%)	22 (15
46–55	617 (22.7%)	459 (21.6%)	128 (26.9%)	455 (21.7%)	336 (20.9%)	51 (21.6%)	42 (29.0%)	441 (21.9%)	324 (21.1%)	51 (21.6%)	42 (29
56–65	545 (20.1%)	404 (19.0%)	114 (23.9%)	435 (20.8%)	315 (19.6%)	63 (26.7%)	33 (22.8%)	417 (20.7%)	297 (19.3%)	63 (26.7%)	33 (22
66–75	445 (16.4%)	325 (15.3%)	96 (20.2%)	408 (19.5%)	301 (18.7%)	60 (25.4%)	27 (18.6%)	396 (19.6%)	289 (18.8%)	60 (25.4%)	27 (18
75+	127 (4.7%)	96 (4.5%)	24 (5.0%)	126 (6.0%)	97 (6.0%)	11 (4.7%)	12 (8.3%)	121 (6.0%)	92 (6.0%)	11 (4.7%)	12 (8.
Summary	Enrollment rate: 8.8%	Enrollment rate: 7.6%	Enrollment rate: 15.4%	Kit/sample return rate: 76.7%	Kit return rate: 75.9%	Sample return rate: 81.4%	Kit return rate: 77.9%	Received a clinical report: 74%	Received a clinical report: 72.5%	Received a clinical report: 100%	Re a cli rep 10

[a] For the participants enrolled via a clinic, 290 provided a blood or saliva sample directly at the clinic after enrollment, whereas 186 received by mail a saliva sample kit.

[b] Phase 1 sample collection was done by a local staff at a patient appointment/encounter.

[c] In phase 2 sample collection, a saliva DNA collection kit was mailed directly to the participant residence by the study team.

[d]All the participants enrolled via a clinic, who either provided a sample directly or mailed their kit back, received a clinical report. One participant provided mo than one sample (3 in total) to get successfully genotype

While the enrollment uptake was higher for the clinic-based outreach cohort (15.4%) when compared to the population outreach approach (7.6%), no significant difference in the rate of samples returned was observed between the different participating cohorts; of note the N was small for the clinic-based cohort (Table 5). Indeed, 75.9% (1,611) of the outreach participants and 77.9% (145) of the clinic-based participants who were mailed a saliva kit to their home address returned their collected sample to the laboratory. A chi-square test of independence showed no significant association between enrollment type and sample return ($X^2(1) = 0.40$, $p = 0.525$). Also, it is worth noting that the type of participating clinic from which the participant enrolled (one specialty

clinic versus two primary care clinics; 45% and 55% of the phase 2 clinic-based cohort, respectively) was not significantly associated with return of a mailed kit ($X^2(1) = 0.32$, $p = 0.572$). However, amongst those participants recruited through population outreach, there was a significant association between race/ethnicity and saliva sample return ($X^2(5) = 17.40$, $p = 0.004$). Post-hoc analyses of standardized residuals with a Bonferroni correction revealed that participants identifying as Hispanic were less likely to return a sample than expected based on an assumption of independence between race/ethnicity and return rates (69% vs. 76% across race/ethnicities, $p = 0.006$). White participants, on the other hand, had higher sample return rates than expected (80%, $p = 0.009$).

WGS Assay Validation of the Inherited Disease and Pharmacogenomics Gene Panels

For the inherited disease genes, the detection of single nucleotide variants (SNVs), indels and structural variants (SVs) by WGS was well correlated with the reference method (next generation targeted sequencing (Invitae)) (data not shown). Results from paired blood and saliva samples were 100% concordant.

For the PGx panel, we observed 100% concordance for *CYP2C19, CYP2C9, VKORC1*, and *CYP4F2* when comparing our training set results with the GeT-RM data for the 18 Coriell samples sequenced (data not shown). The PGx data from the 188 samples of the validation set had very high concordance with the reference laboratory. Since rs12777823 (*CYP2C* cluster), one of the PGx markers assessed for the drug warfarin, was not included in the GeT-RM or Invitae Laboratories PGx panels, the BAM files of the 188 validation set samples were visually inspected to confirm the genotyping results and quality.

Reportable Findings and Return of Results

Overall, based on their Geno4ME genetic results, 21.4% (432/2017) of participants who received a test report had a result with one or more medical intervention recommendations (inherited disease and/or PGx).

Inherited Disease Gene Panel Findings

In total, 158/2,017 (7.8%) of participants who received a report (i.e. had sequencing completed, did not result in QNS or sample failure) had at least one clinically significant finding (P/LP classified variant) associated with an inherited disease and five individuals had two findings (Fig. 2). Despite previous reports of a higher rate of VUS in racial and ethnic minority populations that may limit the identification of actionable results[36], no significant difference in the race/ethnicity distribution of the participants with a positive finding was observed in the Geno4ME study. Three participants were double heterozygous for a P/LP variant in two different genes: 1) *BRCA2* and *CHEK2*, 2) *ATM* and *LDLR*, and 3) *ATP7B* and *KCHN2*. Two participants were compound heterozygous for variants in *ATP7B*. A total of 163 P/LP variants were identified (Fig. 3). A chi-square test of independence found no significant association between race/ethnicity and receipt of a positive (vs. negative) finding ($X^2(4) = 3.99$, $p = .407$; see Fig. 4). Most of the positive findings (91/163, 55.8%) were in a gene associated with an increased risk for cancer(s), and the two genes most frequently reported with identified P/LP variants were *MUTYH* (30 participants, 19%, all heterozygous) and *CHEK2* (18, 11%) (Fig. 3). Of these 18 P/LP findings in CHEK2, 7 were the I157T variant, which at time of study had clinical recommendations for screening and participants were counseled as such,[27,28] at time of publication, this specific variant is now considered by the most recent NCCN Guidelines as a risk allele that does not meet threshold for management change (Genetic/Familial High-Risk Assessment: Colorectal V2.2023 as well as Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V3.2024). While reproductive risk was not a primary focus of the return of results, 71 (44.7%) participants received a positive result solely associated with reproductive decision making/carrier risk (including 30 with a P/LP variant in *MUTYH*, 5 in *NTHL1*, 2 in *MSH3*, 2 in *NBN*, 1 in *VHL* associated with erythrocytosis and polycythemia, 3 in *APOB* associated with hypobetalipoproteinemia, 1 in *LMNA* associated with Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia type A, 7 in *RYR1*, and 20 in *ATP7B*). Of note, at the time of results delivery, NCCN Guidelines suggested that *MUTYH* heterozygotes had moderately increased risk for colorectal cancer and should follow enhanced screening recommendations[28]; at the time of this publication, NCCN Guidelines (Genetic/Familial High-Risk Assessment: Colorectal V2.2023) no longer recommend increased screening for *MUTYH* heterozygotes and therefore we have characterized these findings as “carrier risk” only for analysis purposes. For *ATP7B*, only two individuals were compound heterozygous and had no apparent phenotype associated with Wilson disease. When looking at the enrollment survey (excluding participants whose findings only involved reproductive risk or Wilson disease (N = 73), 45/86 (52%) test-positive participants had no self-reported personal or family history of disease for the associated gene that would meet the threshold for formal risk assessment and genetic counseling referral (cancer/cardiovascular panels) (Fig. 2). For the majority, the lack of personal history of disease could be explained by the participant’s age and/or sex at birth (Table 6). Conversely, 47% (883) and 20% (379) of participants without a positive inherited disease finding self-reported personal and/or family history of cancer and of cardiovascular disease, respectively, which would meet referral threshold. Overall, there was no significant association between having a P/LP variant and meeting threshold for referral for either cancer or cardiovascular disease ($X^2(2) = 4.09$, $p = 0.129$ and $X^2(1) = 0.06$, $p = 0.806$, respectively).

Table 6
Sex at birth and age of participants with no self-reported personal or family history and at least one P/LP findings associated inherited cancer or cardiovascular/connective tissue diseases.

Disease category	Disease	Gene	Gender	Age group
Cancer	BRIP1-related cancers	*BRIP1*	M	46–55
			F	66–75
	CHEK2-related cancers	*CHEK2*	F	18–35
			F	46–55
			M	46–55
			M	56–65
			M	56–65
			F	56–65
			F	66–75
	Colorectal cancer	*APC*	F	46–55
			M	46–55
			M	56–65
			M	66–75
	Hereditary breast and ovarian cancer syndrome	*BRCA1*	M	18–35
		BRCA2	M	36–45
	Hereditary melanoma-pancreatic cancer syndrome	*CDKN2A*	F	46–55
			M	56–65
	Lynch Syndrome	*MSH6*	F	46–55
		PMS2	F	66–75
	Paraganglioma-pheochromocytoma syndrome	*SDHB*	M	18–35
			F	56–65
	Von Hippel-Lindau syndrome	*VHL*	F	76+
Cardiovascular and connective tissue	Arrhythmogenic right ventricular cardiomyopathy	*PKP2*	M	18–35
			M	18–35
	Arrhythmogenic right ventricular cardiomyopathy Dilated cardiomyopathy	*DSP*	F	36–45
	Familial hypercholesterolemia	*APOB*	M	46–55
			M	56–65
			F	56–65
		LDLR	F	36–45
			F	36–45
			M	36–45
			F	46–55
			F	56–65
			M	66–75
			F	76+
		PCSK9	F	36–45
	Hypertrophic cardiomyopathy	*MYBPC3*	M	46–55
			F	56–65
	Hypertrophic cardiomyopathy	*MYL2*	F	56–65
	Hypertrophic cardiomyopathy, Dilated cardiomyopathy	*MYH7*	M	36–45

Disease category	Disease	Gene	Gender	Age group
		TNNI3	F	36–45
	Long QT syndrome type 1, Short QT syndrome	*KCNQ1*	F	56–65
	Long QT syndrome type 2 ,Short QT syndrome	*KCNH2*	M	36–45

PGx Findings

A PGx finding was defined as "immediately actionable" when the participant reported taking one of the supported medications (Table 2) at enrollment and had a PGx result associated with an increased risk of side effects or decreased drug efficacy for that medication for which a clinical recommendation is available. Of participants who received results, 294/2,017 (14.6%) had an immediately actionable PGx finding (one participant had two actionable findings). When looking at the different drug classes that are part of the PGx panel, 82% of these immediately actionable findings were related to proton pump inhibitors, 13% to antidepressants (selective serotonin reuptake inhibitors, SSRIs), and 5% to anticoagulants/antiplatelet agents (Table 7). Of note, regardless of their answer to the medication questionnaire at enrollment, all participants received a PGx report with at least one recommendation that could impact their care management at some point in the future when considering the seven likely prescribed drugs included in the panel (Fig. 5).

Table 7
Distribution of the immediately actionable PGx finding per drug class.

Drug class	Number of immediately actionable PGx
Proton pump inhibitors	242
Selective serotonin reuptake inhibitors	39
Anticoagulants/antiplatelet agents	14

Return of Results Follow Up

All providers were electronically notified of the availability of their patients' results (positive or negative) through an electronic EHR notification at resulting. All results included a provider cover letter which included a link to the provider portal for additional clinical resources. For patients with a positive inherited disease result, providers were additionally notified of the patient's finding by outreach from a study coordinator. Of 158 participants with a P/LP variant in the inherited disease panel, 154 were referred to genetic counseling services by the study; 4 participants declined referral through the study as they were already being followed elsewhere by clinical genetics. Utilization of telehealth genetic counseling services via Genome Medical for participants with a P/LP variant was generally high, with 88% (136/154) of referred individuals scheduling a telehealth appointment after referral and of those, 88% (120/136) completing an appointment (Table 8). Although the N is small, there were no significant differences in the demographics of all individuals referred for a P/LP finding compared to those who completed the genetic counseling appointment (Table S1).

Table 8
Status of genetic counseling referrals for Geno4ME participants with P/LP results on inherited disease panel.

Appointment Status	Participants with P/LP results (n = 158)
Referred	154 (97%)
Scheduled	136 (88%)
Completed	120 (88%)

Discussion

The field of genomic medicine is at a key inflection point where advances in sequencing speed and diminution of cost combined with scalable digital cloud platforms can now enable population-scale clinical sequencing. Eighty-four percent of hospitals in the United States are community hospitals (AHA Fast Facts on US hospitals, 2024); integrating genomics into routine community healthcare represents a significant opportunity to achieve greater access for patients at population scale. To deliver on this promise, programs must be scalable, efficient, and equitable. With Geno4ME's core program delivery, we attempted to specifically address issues of recruitment of diverse populations in genomics research, establishment of WGS as a mechanism for clinical assessment and integration, development of scalable digital tools and processes that require minimal to no on-site clinic staff for cohort enrollment, and education for patients and providers. Given Providence's breadth as a community health system and the unique challenges and opportunities this posed for Geno4ME implementation, we offer lessons learned from the development of this pilot program that can be leveraged for future work.

Our Geno4ME enrolled population was comprised of 47.5% of individuals who self-identified as racial or ethnic minorities and spanned across 5 states (CA, OR, WA, MT, and AK). Effort was made to outreach to individuals who identified as being of Hispanic ethnicity or as Black or African American, Asian, or another non-White race; those who had Medicaid coverage; those who resided in rural areas; and those whose primary language in the EHR was Spanish.[19] The study was also launched during the COVID-19 pandemic, which necessitated novel methods of consent and biospecimen collection that enabled participants to engage with clinical care and research from home. Previously established population genomics programs in the US have successfully recruited patients for genomics biorepositories and return of results; within health systems programs, such as the Geisinger MyCode and Sanford Chip programs, approaches to recruiting and enrolling participants have typically been "warm touch" including engagement of provider champions in the local

health system, development of new clinical care pathways, and local recruitment by on site study staff.[8,37–44] However, programs like Geisinger's and Sanford's that are deeply embedded in the care network have been localized to one state/region, potentially limiting the conclusions that can be drawn about ideal approaches to engaging diverse participants and providers in genomics research across multiple care settings and geographies. The All of Us Research Program is a nationwide program that spans multiple care settings and geographies, but it is a public research program, rather than initiated within a particular health system, and thus disconnected from a participant's actual care network. Additionally, programs such as the Healthy Oregon Project and the Healthy Nevada Project, which involved close partnerships between hospitals and research entities, invested in on-location study personnel and statewide marketing campaigns; these were also limited to one geographic area and a health system in that region. In Geno4ME, despite provider outreach and engagement that supported phase 1 of clinic-based recruitment, achieving recruitment and buy-in from multiple clinics and champions across the multi-state community health system was ultimately less scalable and efficient compared to direct outreach to patients themselves with supplementary education to providers, due to the number and breadth of clinics and affiliates within the health system (over 1,000 clinics and 30,000 providers). This approach was largely enabled by the phase 2 population outreach and at-home saliva sample collection. While the "direct-to-patient" approach in phase 2 had a lower uptake of study enrollment compared to the "warm touch" of clinic-based recruitment that involved a trusted provider presenting the study opportunity to patients (7.6% vs. 15.4%, respectively), phase 2 approaches were more scalable, enabled us to reach younger participants of more diverse backgrounds, and resulted in comparable sample return rates and engagement with study-covered genetic counseling.[19] To fully realize the benefits of population genomic screening, the ability to reach younger populations is particularly important, as screening for CDC Tier 1 conditions has been demonstrated to be cost-effective in adults under 40 years of age.[45] We did observe that individuals who identified as Hispanic were less likely to return a sample while White participants were more likely to return a sample. Future studies should examine the possible reasons why participants may change their minds about completing genetic testing after enrollment and factors that may further explain the differences between these groups, such as trust in the research process, perceived importance of genetic results, preferred language, logistics like access to a postal mailbox, or others.

Of note, because we initiated outreach in WA, MT, and AK later than in CA and OR, our volumes of patients recruited from WA, MT, and AK are lower overall, but patterns of engagement were consistent across all regions.

Additionally, all our consenting took place via a custom-built and novel e-consent platform, with no paper forms or in-person research coordinator visits to facilitate consent. These findings suggest that population-based outreach is a scalable method to engage a broad population of participants in genetic screening provided the right tools are in place to support education and informed consent, and should be considered for future programs. For some populations, a trusted provider may motivate the initial desire to participate in genetic screening; however, after initial engagement and enrollment, the involvement of the provider did not appear to have a significant impact for the participant providing a sample and completing testing. In the future, programs should also develop resources to aid providers in discussing the potential benefits of genetic testing with patients and/or referring them to appropriate genetic counseling resources. Creating multiple opportunities for patients to hear about genetic testing from trusted sources such as their primary care providers or clinic staff may facilitate engagement.

On our return-of-results panel, we chose to include genes associated with cancer, cardiovascular disease, and pharmacogenomics; for inherited diseases, we curated a panel that included moderate penetrance genes defined in NCCN Guidelines in addition to those genes recommended by the ACMG to return as secondary findings from sequencing results. Pathogenic variants in genes on the inherited disease panel were detected in 1 of every 13 participants and every patient had a PGx genotype that could impact their current care or care in the future (while 14% had an immediate benefit); these findings emphasize the power of including multiple disease areas in testing panels for the greatest impact on patient care. Combined with the introduction of EHR alerts and clinical decision support, this represents a powerful tool for intervention at key care points such as when a prescriber is considering a drug that is incompatible with the patient's pharmacogenetic profile.

Additionally, population screening of an unselected cohort in our program revealed P/LP variants in 52% of participants who had no reported personal or family history of the associated disease that would meet the threshold for detailed risk assessment and genetic counseling (cancer or cardiovascular disease only). While patients with a personal or family history of disease may be more likely to be interested in enrolling in a genomic screening study like Geno4ME, other population sequencing initiatives have found that between 35–75% of participants reported no relevant personal or family history of disease and/or had no such history documented in the EHR prior to receiving a genetic diagnosis through the screening program. [8,39] Taken together with our findings, this indicates potential inconsistencies in how personal and family history are reported by patients and documented by clinicians. The lack of family history in a quarter of mutation carriers also suggests that a proactive population testing approach may be an effective option to identify individuals with pathogenic variants rather than relying on family history-based screening methods alone. Interestingly, in our program, nearly two-thirds of participants of participants *did* report a positive personal and/or family history of cancer and/or significant cardiovascular disease prior to joining the study. However, this was based on participant self-report on a screening questionnaire rather than formal pedigree collection or EHR data. Furthermore, of patients who were negative for P/LP variants, t least 50% had personal and/or family history that may still warrant personalized risk management and care recommendations. Though not covered by the study screening, Geno4ME indicated to providers on the cover letter of results report which participants had reported this personal or family history and suggested genetic counseling for further formal risk assessment and management recommendations. While many genetic screening programs aim primarily to identify high-risk mutation carriers, future programs should aim to also address the empiric risks of individuals with no P/LP variant but positive personal or family history to facilitate discussion with the patient about a more comprehensive assessment of their health risks. Incorporation of polygenic scores may also be an area of future exploration.

On the inherited disease panel, we chose to include certain conditions that could potentially present with late-onset symptoms and recessive conditions where heterozygous carriers may also have moderate disease risks, such as Wilson disease, *MUTYH* heterozygotes, and *RYR1*-related myopathies. Moderate risk genes on the inherited disease panel are subject to continued changes in risk interpretation. For example, *MUTYH* heterozygotes as well as the CHEK2 I157T variant are now considered by NCCN Guidelines (Genetic/Familial High-Risk Assessment: Colorectal V2.2023 as well as Genetic/Familial High-Risk

Assessment: Breast, Ovarian, and Pancreatic V3.2024) to not confer increased cancer risk and to not change screening timing or initiation. If programs choose to include moderate risk genes, a mechanism to readily convey new modified risk information is essential; our platform allows for not only storage, review, and retrieval of results, but also a communication interface and process for referral to genetic counseling should risk interpretation change. Another consideration for our program and future programs is whether to return results associated with reproductive risk only. Although our overall N is small, only 2 participants were *ATP7B* compound heterozygotes compared to the 21 *ATP7B* carriers we detected; we also observed 7 variants in *RYR1*, none of which had a clear association with malignant hyperthermia. Based on our results, we would suggest that genomic sequencing programs that wish to return screening findings that are primarily applicable to the adult participant themselves should not include *ATP7B* and could consider only returning the variants associated with specific diseases.

Critically important, every participant had at least one PGx finding that could impact their care management at some point in the future when considering the seven commonly prescribed drugs included in the panel. This highlights the significant impact of PGx results and the importance of building clinical infrastructure that can support the use of these results in patients' care throughout their life; we suggest the inclusion of PGx data in all future population genomic screening programs. Our program involved manual pharmacist medication reconciliation alongside the patient's genomic results and clinical history, which was successful for provider uptake of PGx-guided therapy recommendations, but is not scalable beyond this pilot when considering implementing PGx in routine care settings.[46] To this end, we have implemented clinical decision support software in our EPIC EHR to dynamically manage PGx data over time and provide useful info to providers when needed. Our preliminary data suggest that provider uptake of PGx-recommended therapy adjustments is high for the medications that Geno4ME participants reported "currently taking" at enrollment; further research is needed to understand the utility of PGx for guiding future medication therapy adjustments.

A key element of our program delivery is the change in patients' care due to increased access to genetic testing and integration of genetic results into the patients' routine clinical care. An important aspect of this is downstream care utilization and close communication with the patient's routine care team. While the longitudinal follow up is still ongoing, utilization of telehealth genetic counseling services by participants with a pathogenic variant was generally high across all those referred. Pre-test education and expectation-setting via our novel e-consent and education platform, in addition to the post-test follow up by the study team and genetic counselor, may have contributed to this high follow-up rate. Building upon the gene-specific fact sheets available to providers, future work will focus on integrating patient results and clinical decision support more directly into providers' existing EHR workflows for ease of use.

Limitations

The design of Geno4ME had some limitations. While thousands of patients were outreached in Geno4ME, the enrollment rate for Geno4ME in the outreached population across different outreach strategies was low (15.4% for clinic-based outreach versus 7.6% for virtual outreach). While these rates mirror enrollment rates for other population genomics studies, they also represent a key bottleneck in the overall transition to full participation in genome-guided healthcare. Despite the promise of free clinical WGS testing and access to counseling and education, there is still a clear gap in desire to participate in such a study, likely driven by multiple factors including perceived lack of value or connection between genomics results and their routine healthcare, fear or apprehension regarding potential findings, or potential concerns over genomic data privacy. As such, a key aspect of our future work will be focused on better understanding those barriers and developing strategies to increase engagement in genomic medicine. Moreover, we also did not allow for patients to opt out of receiving a clinical report from the study, which contained risk information for inherited diseases including cancer, cardiovascular disease, and others. Our clinical panel was also broader than CDC Tier 1 conditions (CDC Genomics Implementation). This may have limited participation by individuals who did not wish to receive broad clinical risk information but who otherwise may have been interested in contributing their genomic data to research. Future programs could consider offering different "tiers" of Return-of-Results.

We recognize that reliance on electronic tools for scalability, such as our novel e-consent platform, limits participation for some individuals and could impact diversity and inclusion within some communities as it requires access to a computer or smartphone (Pew Research Center, Mobile and Internet, Broadband Fact Sheets). In the future, outreach development strategies assessing differing technological capabilities and limitations should be assessed. Additionally, our clinic-based recruitment was limited to only 3 clinics, and recruitment strategies were opportunistic rather than stratified random sampling. Therefore, the patients who took part via clinics may not be representative of the broader Providence patient population, and comparisons between the two outreach approaches and the effect of provider engagement may be limited. In the future, stratified random sampling should be considered within a clinic population eligible for Geno4ME.

State-of-the-art technology available at the time of the first phase of Geno4ME (NovaSeq 6000) still had limitations in cost and scalability for WGS analysis. While these bottlenecks will likely be reduced by more recent technologies (e.g. NovaSeq X Plus, Ultima UG100, etc.), better cost and throughput for sequencing alone will not reduce the downstream need for experts-in-the-loop for genome interpretation. While efficient tertiary interpretation solutions can aid this process, there is still a dearth of trained experts in the field for variant interpretation and genetic counseling to fully support a future state where a genome is a fundamental component of all patients' healthcare. Given that there is currently limited or no insurance reimbursement of clinical WGS or reanalysis for asymptomatic patients (screening program), there is a lack of sustainability that can create disparities in access if labs choose a patient billing model.[47,48]

Return of results for both inherited conditions and PGx were not discrete data integrated into EHR but were PDF reports that resided in the "Media" tab of the EHR (EPIC). This required providers and participants to be aware of PGx results for future states and medication ordering. We have remedied this challenge with implementation of the EPIC Genomic Indicator Module (EGIM) across our health system. Now, historical results from Geno4ME are stored discretely in the EGIM along with other genetic reports, enabling improved visibility and clinical decision support for providers.

Finally, there is still little-to-no portability for genomes in healthcare. While some pathways exist for limited EHR-to-EHR communication (e.g., EPIC CareEverywhere), the current promise of a whole genome sequence that is utilized throughout a patient's lifetime is tempered by the fact that if a patient chooses a different health care network, there is no current model for ensuring that the patient's WGS data travel with them. Solving this bottleneck will undoubtedly require a larger initiative of stakeholders from across public and private healthcare and novel data management systems that can interface with a wide variety of EHR systems and maintain security and patient identity throughout.

Future Directions

Longitudinal follow up of participants in Geno4ME is ongoing. We plan to collect and analyze longitudinal health behaviors, participant-reported health outcomes, and the intersection of genomic and social determinant risk factors in the coming years. Also, the availability of patients' genomic data enables long-term use of their results over their lifetimes as Providence patients. We aim to continue to leverage participants' WGS data to include additional PGx gene-drug pairs and other inherited disease risk genes over time. We see Geno4ME as both a study and a platform for ongoing engagement with patients about their genomic data with a major goal of increasing literacy around precision medicine and utility of results at the right point in the care continuum; with that goal in mind, Geno4ME is a model system for facilitating a patient-provider dialog around genomics through continued updates and potential expansion into other results such as polygenic risk scores. Through this work, we continue to build an evidence base for what we predict will be the future state of healthcare, where genomic medicine is truly accessible to all.

Declarations

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Author Contributions

The manuscript was written by I. A. L. B. and K. R. E., with critical input from O. K. G., and B. D. P. The study was designed by the five principal investigators, O. K. G., C. B. B., A. T. M., B. D. P., and K. V. with support from J. C., E. D., K. R. E., K. J., I. A. L. B, J. C. L., E. R., and K. T. Project administration was led by J. C., K.R. E., M. B. C., and JB R. The study data were analyzed by I. A. L. B. and J. T. W. with support from K.R. E. The recruitment material was designed by I. A. L. B., K. J., K. R. E., and JB R.; I. A. L. B., K. J. , and K.R. E. worked on provider/patient education material. The front-end portion of study website and the e-consent was developed by L. A. and A. K. created all the graphics and designs for the education and recruitment material. L. D. and K. G. J. designed the population outreach recruitment strategy with oversight by K. V., and provided some data analysis. N. W., K. J., I. A. L. B, and K.R. E. designed the clinical report with the support from J. T. W. The curation of the variants for inherited diseases was done by I. A. L. B. and J. T. W.; I. A. L. B. developed the PGx test panel and K. O. developed the PGx variant caller in the Fabric Genomics cloud platform. J. T. W. and J. W. performed the WGS test validation and routine WGS. J. W., with support from M. M. M. and M. J. R. oversaw the variant confirmation process with the external laboratory. M. B. C. and B. D. P. oversaw the sequencing lab operation. B. A. C. and E. M. S. provided bioinformatic support. B. S. and H. V. created and maintained the participant database with oversight by A. T. M. PGx pharmacist consult to participants and providers were conducted by L. C. Y. The graphical design of the figures and the abstract was done by A. K. D. Statistical analysis was performed by B. B.

Declaration of Interests

K. T. is a current employee of Illumina, but during her involvement with the study, she was affiliated with ISB. Erica Ramos is a current employee of and shareholder in Genome Medical, Inc. Genome Medical was paid to consult on this project and is a paid provider for the gene-specific fact sheets and telehealth genetic counseling. M. G. R. is a founder, employee, and shareholder of Fabric Genomics. K. O. is the founder and employee of Genetic Intelligence Inc. and works as a consultant for Fabric Genomics.

Web Resources

Geno4ME study website, https://www.geno4me.org

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines, https://cpicpgx.org/guidelines/

FDA, Table of Pharmacogenomic Biomarkers in Drug Labeling, https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

AHA Fast Facts on US hospitals, 2024, https://www.aha.org/system/files/media/file/2024/01/fast-facts-on-us-hospitals-2024-20240112.pdf

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal V2.2023. © National Comprehensive Cancer Network, Inc. 202X. All rights reserved. Accessed [7/11/2024]. To view the most recent and complete version of the guideline, go online to NCCN.org.

https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic: Colorectal V3.2024. © National Comprehensive Cancer Network, Inc. 202X. All rights reserved. Accessed [7/11/2024]. To view the most recent and complete version of

the guideline, go online to NCCN.org.

https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

CDC Genomics Implementation, https://www.cdc.gov/genomics/implementation/index.htm

Pew Research Center, Mobile Fact Sheet, https://www.pewresearch.org/internet/fact-sheet/mobile/ Pew Research Center, Internet, Broadband Fact Sheet, https://www.pewresearch.org/internet/fact-sheet/internet-broadband/

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Figures

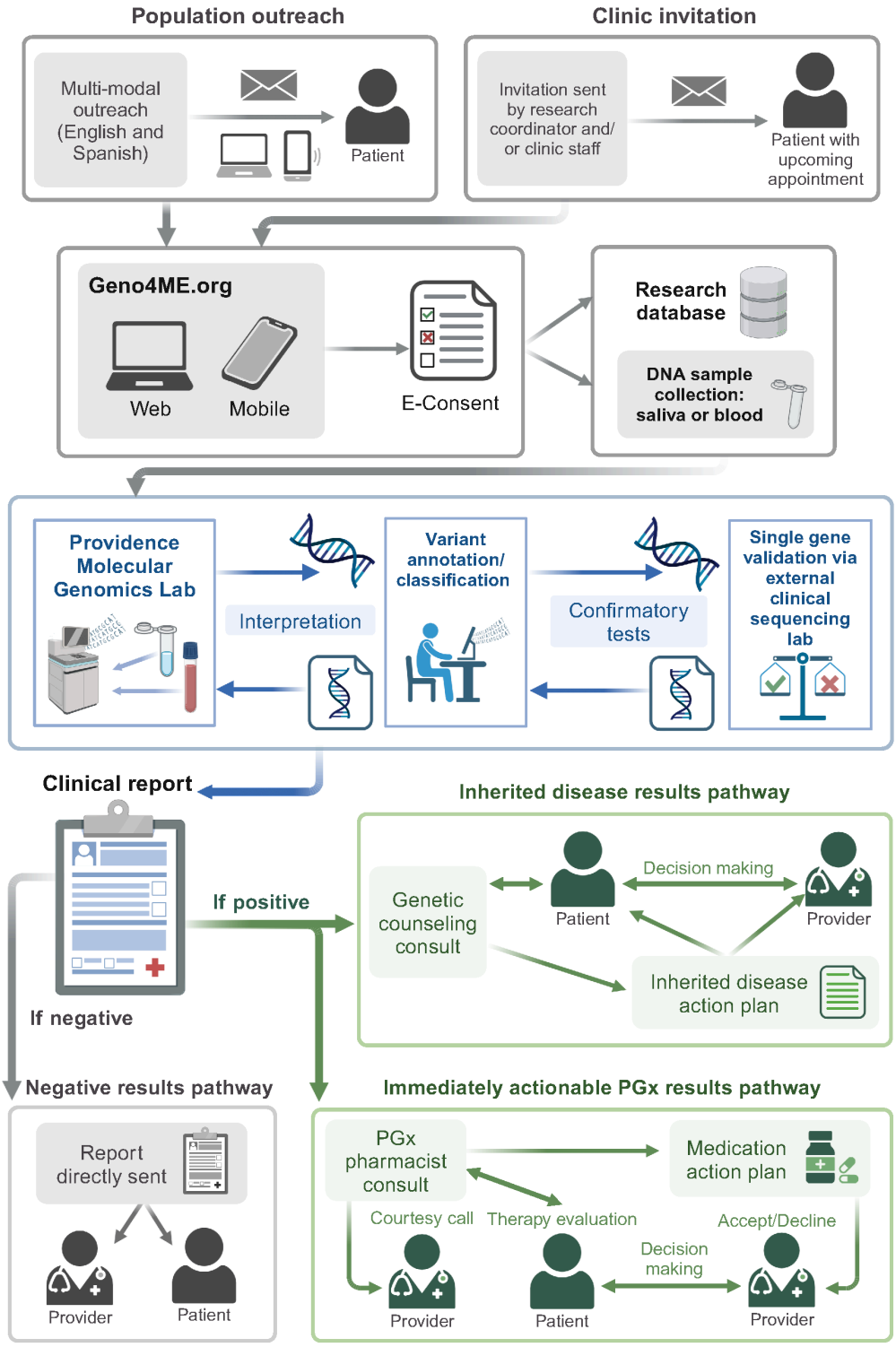

Figure 1

Geno4ME workflows, patient journey, and study process

This figure illustrates the different steps of the Geno4ME. It espcially highlights the two different recruitment approaches (population outreach and clinic invitation), the DNA sequencing/analysis workflow, and the return of results for positive results.

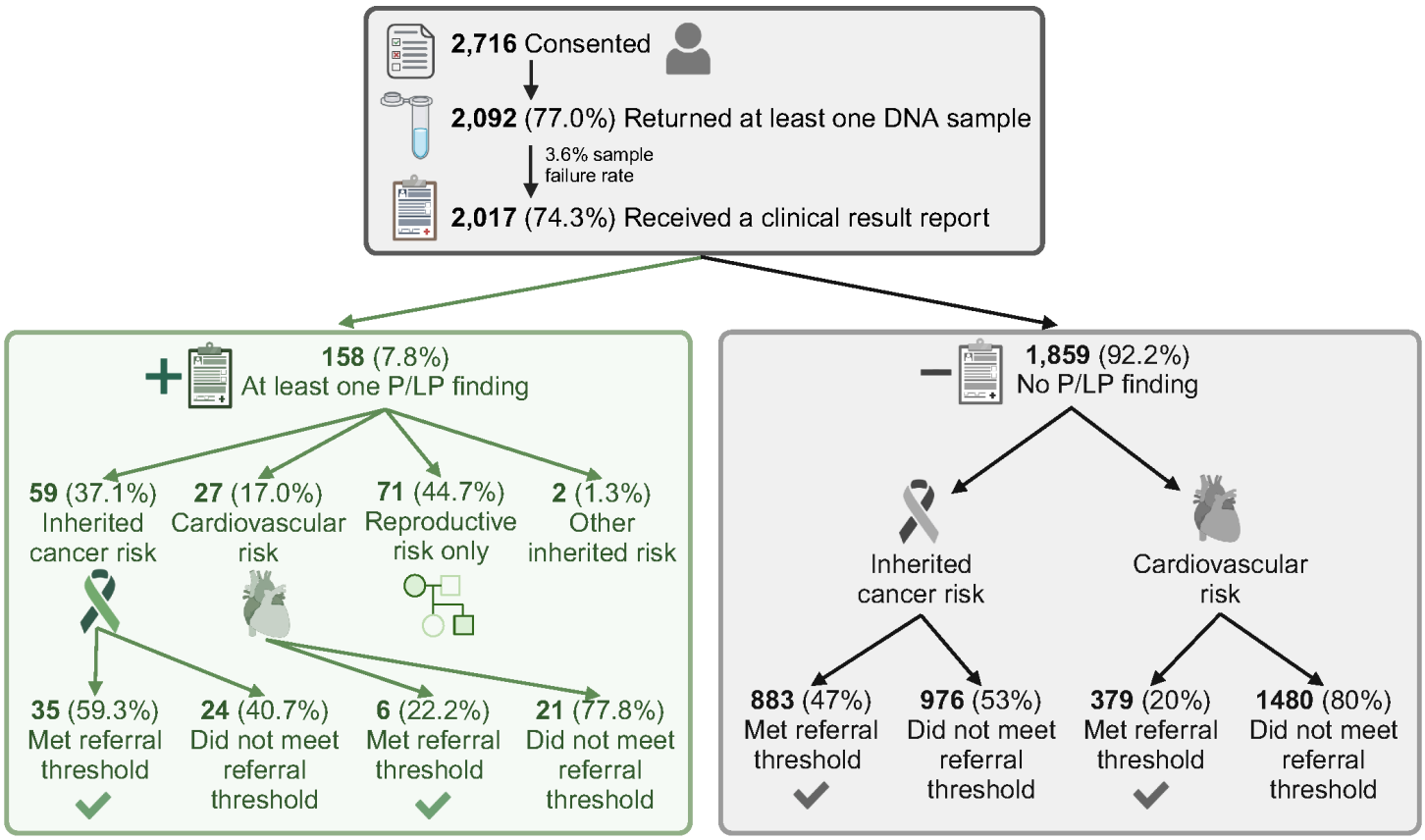

Figure 2

Geno4ME inherited disease findings and self-reported personal and/or family history

The top box recapitulates the numbers of participants who consented, provided at least one DNA sample, and received their clinical report (i.e. had sequencing completed). For the 2,017 participants who received a clinical result report, the two bottom boxes provide the number of reports with at least one pathogenic/likely pathogenic (P/LP) finding (left green box) or no P/LP finding (right light gray box). The P/LP findings are grouped by type of associated disease. The number (percentage) of participants who self-reported during enrollment personal or family history of the associated disease that would meet (or not meet) the threshold for detailed risk assessment and genetic counseling is indicated for each group of participants (cancer or cardiovascular disease only).

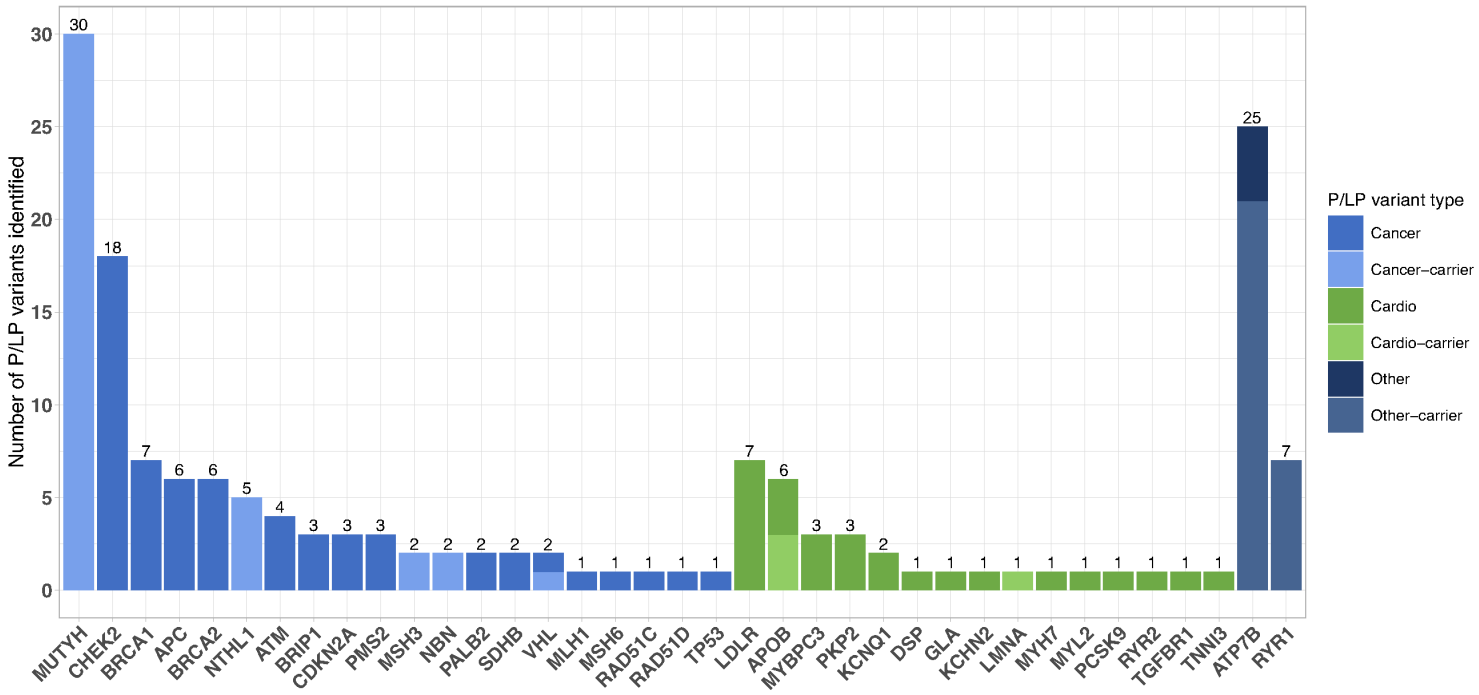

Figure 3

Distribution of pathogenic and likely pathogenic variants identified in the genes included in the Geno4ME inherited disease panel

This bar graph displays the number of pathogenic and likely pathogenic (P/LP) variants identified in genes associated with increased risk of cancer (total N=100, with 60 variants associated with an increased risk for the participants in medium blue, and 40 identified as carrier risk only in light blue), cardiovascular and connective tissue diseases (total N=31, with 27 variants associated with an increased risk for the participants in medium green, and 4 identified as carrier risk only in light green), and other (total N=32, with 4 variants associated with an increased risk for the participants in dark blue, and 28 identified as carrier risk only in very dark blue). In total 163 P/LP, were identified and confirmed by the external reference laboratory. Of note, for *VHL*, one variant (in light blue) was only associated with autosomal recessive erythrocytosis and polycythemia, for *APOB*, 3 variants (light green) were associated with hypobetalipoproteinemia, and for LMNA, 1 variant was associated with Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia type A (light green).

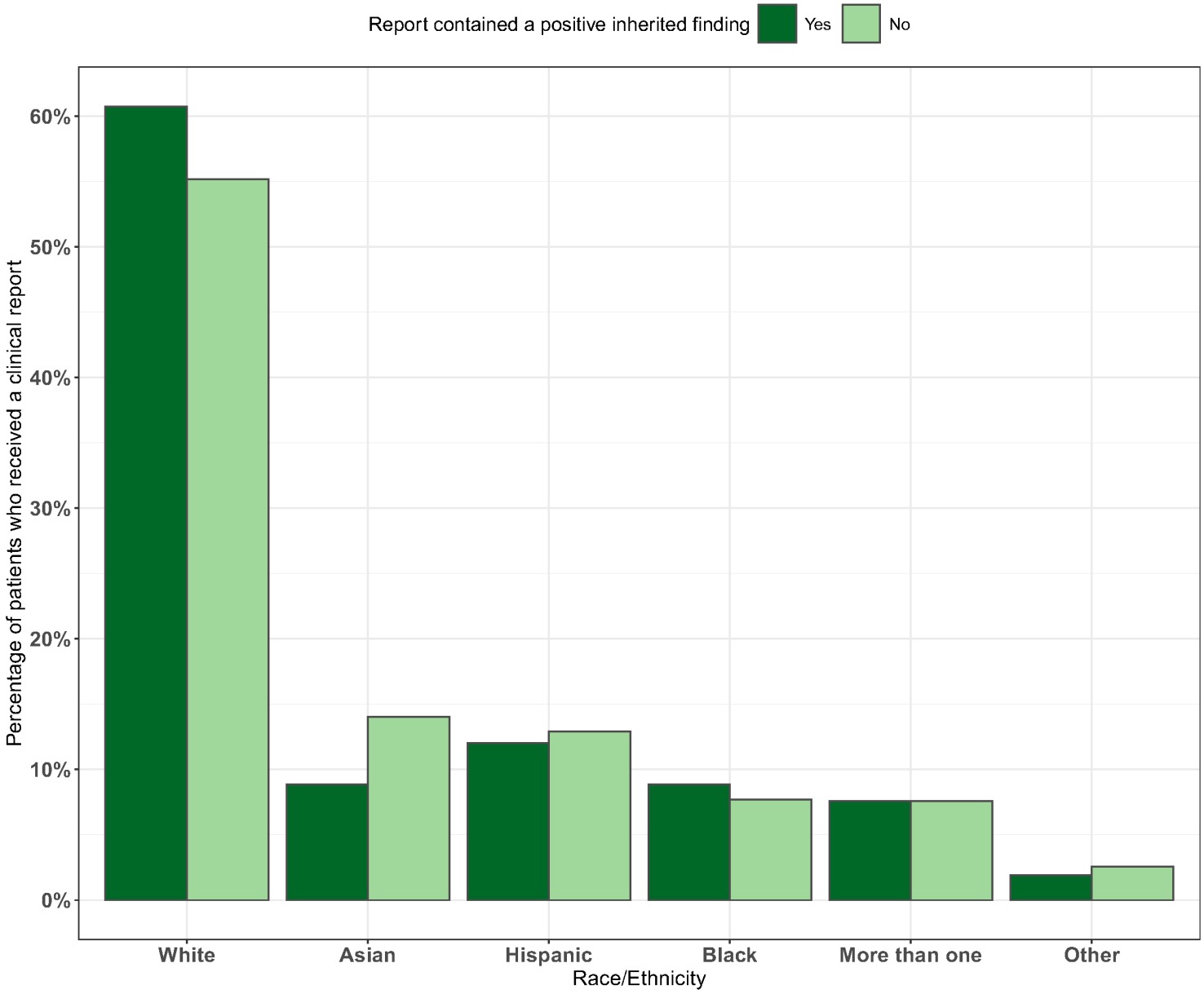

Figure 4

Race/ethnicity of the participants who received a clinical report with or with a positive finding for one of the genes included in the Geno4ME inherited disease panel.

This bar graph shows the ethnic/race distribution of the 158 participants (dark green) who had one or more P/LP variant (positive finding) for one of the genes associated with an inherited disease and of the 1,859 participants (light green) who had no P/LP finding. The percentages are calculated within each group (i.e. with or without a positive finding).

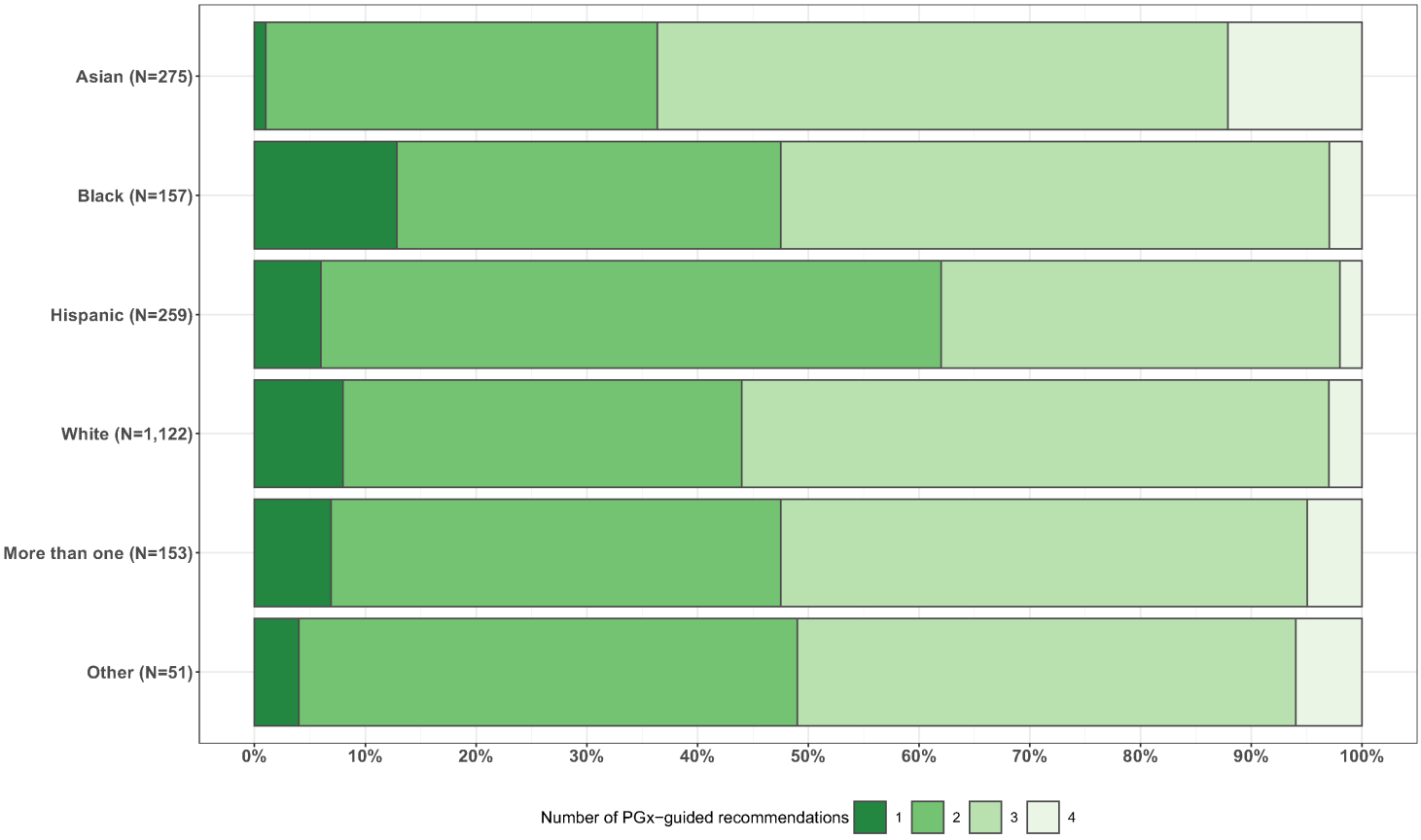

Figure 5

Distribution the number of PGx-guided recommendations reported for all Geno4ME participants who received a clinical report.

The bar graph shows, for each self-reported race/ethnicity, the percentage of participants who received 1 (dark green), 2 (medium green), 3 (lighter green), or 4 (lightest green) PGx-guided recommendations in their Geno4ME clinical report. The number of identified PGx recommendations per participant reported in this graph is regardless of their answer to the medication questionnaire from enrollment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalInformation.docx