Geographical Access, Implementation Experience, and Patient Perception of Genetic Testing in the United States

by

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
AHRQ	Agency for Healthcare Resource and Quality
CDC	Center for Disease Control and Prevention
CDS	Clinical Decision Support
CFIR	Consolidated Framework for Implementation Science
CILA	Clinical Laboratory Improvement Amendments
CPIC	Clinical Pharmacogenetics Implementation Consortium
DPWG	Dutch Pharmacogenetics Working Group
DTC	Direct-to-consumer
EHR	Electronic Health Record
GIS	Geographic Information System
GTR	Genetic Testing Registry
HCT	Hematopoietic Cell Transplantation
HINTS	Health Information National Trends Survey
IGNITE	Implementing Genomics in Practice
IPA	International Pharmaceutical Abstract
NCI	National Cancer Institute
NHGIS	National Historical Geographic Information System
NIH	National Institute of Health
NGS	Next Genome Sequencing
PharmGKB	Pharmacogenomics Knowledge Base
PGx	Pharmacogenetics
PMI	Precision Medicine Initiative
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QoL	Quality of Life
TPB	Theory of Planned Behavior
TRA	Theory of Reasoned Action
US	United States
WGS	Whole Genome Sequencing

Abstract

Background and Significance: Genetic testing is thriving, and its impact on human lives is enormous. However, the slow uptake of genetic testing into routine clinical practice indicates that much remains to be explored with regards to finding the best ways to facilitate the implementation process.

Objective and Specific Aims: The purpose of this study is to conduct a comprehensive analysis regarding access to genetic testing centers, implementation issues, and public awareness, perceptions, and preferences towards genetic testing concepts and strategies involving large minority groups as well as rural populations. This study used a road network analysis, a scoping review, and a Qualtrics survey to address **three specific aims**: 1) to examine the geographical access to genetic testing centers for people living in the United States, 2) to synthesize current evidence on the barriers and facilitators to implementation of pharmacogenetic testing in a healthcare setting, and 3) to assess the awareness, perceptions, and preferences toward genetic testing among the United States general public, and how this may vary by racial-ethnic group and rural-urban status.

Methods: For aim 1, genetic testing center addresses were collected from the American College of Medical Genetics and Genomics (ACMG) website and then geocoded the genetic testing center locations as *destinations* using ArcGIS address locator. The centroid points were calculated for each US census tracts and set them as *origins*. Then, a road network analysis of travel times was performed between origin and destination using closest network facility analysis feature in ArcGIS online ready-to-use services. A descriptive summary of the total US

population by travel times categories i.e., less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes, and 180 minutes and above was presented. Chi-square tests were used to compare the differences between racial groups by travel time categories.

For aim 2, a scoping review was conducted with an expanded literature search using Ovid MEDLINE, Web of Science, International Pharmaceutical Abstract (IPA), and Google Scholar to look for any studies reporting implementation of pharmacogenetic testing in a healthcare setting, from a health systems perspective. Articles were screened using the DistillerSR and findings were organized using the five major domains of Consolidated Framework for Implementation Research.

For aim 3, we developed a survey questionnaire using Health Information National Trends Survey (HINTS) and Theory of Planned Behavior constructs. We used a Qualtrics panel to recruit a total of 1,600 members of the US general public to respond to our survey. Comparisons between different racial-ethnic groups and rural-urban respondents for awareness and preference sections were made using chi-square tests. For the perceptions domain, logistic regression models were used while dichotomizing the dependent variable "intention to get a genetic test" into low intention (less than median score) and high intention (median and above).

Results and Implications: Findings from our road network analysis revealed that more than 3 million people in the United States, around 1% of the total population, had to drive 180 minutes or more to the nearest genetic testing center. In addition, 58% of Whites had to drive less than 30 mins to the nearest center, while significantly higher percentages of Blacks (73%) and Asians (82%) had similar distance to travel.

One striking finding from our scoping review is that the majority of barriers and solutions to the implementation of pharmacogenetic testing in healthcare settings surrounded intervention

characteristics and inner settings. Factors relating to cost and reimbursement were described as a major barrier in the intervention characteristics. Another two major barriers identified in our scoping review were the lack of utility studies to provide evidence for genetic testing uptake and technical issues such as integrating genetic information to medical records. Our findings suggest that long term program evaluations are required to verify the role of the discussed factors in the uptake of genetic testing across different healthcare settings using rigorous methods.

Findings from our Qualtrics survey revealed that respondents were aware of genetic testing and understood its role around risk of disease and inheritance, but half of the total respondents were not aware of genetic testing in the context of choice of treatments, identifying adverse events, and dosage correction. Participants preferred to share their test results with doctors and genetic counselors over pharmacists. But they were not comfortable sharing the results with employers and health insurance providers. Statistically significant differences between different racial and ethnic groups as well as the rural-urban populations were observed across different survey questions.

Overall, access to genetic testing clinics is still a hurdle for people living in some specific states as well as Whites compared to Blacks and Asians living in the US. Barriers and facilitators identified in this scoping review should act as a checklist for future implementation since the findings are comprehensive and reported based on an implementation framework. More educational resources and trainings are required for all different stakeholders including prescribers, pharmacists, and patients to increase genetic testing uptake among the general population in the US.

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Chapter One

Introduction

1.1 Background, Rationale, and Significance

Hope was skyrocketing when the first draft sequence of the human genome was published. In 2001, the National Institutes of Health (NIH) Director Francis Collins predicted several key points, including new drug targets, individualized preventive medicine based on genetic risk, use of pharmacogenomics to improve drug therapy outcomes, and mainstreaming of genetics into the routine clinical care for the future of genomic medicine.[1] Although Collins et al. insisted that the predictions have come true to some extent, all those were viewed as too optimistic by the year 2010.[2] Later, a systematic review on the implementation science in genomic medicine reported that although this field has enormous potential to improve human health, the real-world implementation of genomic medicine and its impact is severely lacking.[3] This review identified several opportunities, including implementing evidence-based precision medicine in real-world settings, using implementation science frameworks, and incorporating all different stakeholders in genomic research to advance the field of genomic medicine.[3]

In 1993, the National Academies of Sciences, Engineering, and Medicine report defined access as, "the timely use of personal health services to achieve the best possible health outcomes".[4] Lack of access to healthcare services is associated with increased risk of poor health outcomes.[5,6] A systematic review found transportation barriers including vehicle inaccessibility and mode of travel, differences in urban and rural geographic location, and travel burden by time and distance to be important barriers to healthcare access.[7] Distance from the hospital was found to negatively impact cancer patients diagnosis, treatment plan, prognosis, and overall quality of life (QoL).[8] A study on breast cancer patients in South Dakota reported geographic proximity to

treatment facilities was instrumental in treating these patients because longer distances to the facility resulted in greater geographic obstacles to access.[9] Longer driving distance was associated with less use of insulin and poor glycemic control.[10-12] Travel time was also considered as an important predictor in early diagnosis of mental health disorders and use of psychiatric outpatient clinic services.[13,14] Another article recently examined population based geographic access to National Cancer Institute (NCI) cancer center facilities and found more that 33 million individuals living in the United States (US) have potential access to a NCI cancer center within an hour driving time.[15] However, geographic access was limited for rural residents and a few race/ethnic groups such as Hispanics and Native Americans. Such assessment for genetic testing centers examining the access to care does not exist to this date. Hence, it is important to characterize geographic access to genetic testing centers for people living in the US, overall and by demographic characteristics.

Genetic research has shifted the idea of "one size fits all" to more personalized approaches to medical treatment, which saves time and money.[16] One of the ultimate goals of genetic testing is to select the best treatment regimen for each specific individual designed to improve their health status. Several studies have reported the benefits of genetic testing on different clinical outcomes such as reduced cost, reduced hospitalization, improved adherence, improved efficacy, and safety.[17] Although the benefits of genetic testing in drug efficacy and safety are already established, the application into routine clinical practice remains limited.[17] Previous studies have reported several challenges about integrating genetic testing into routine care, including limited availability of rapid genetic tests, the complex nature of gene knowledge, implementing clinical decision support (CDS) tools, incorporating genetic information in the electronic health record (EHR), the large size of genomic data, storage capabilities, cost-

effectiveness, and insurance coverage.[18,19] Among all these factors, it is unknown whether a single component is largely responsible for such low implementation in routine care. In addition, these previous studies attempted to outline the challenges in the implementation of genetic testing and its solutions, either from an individual or institutional perspective.[18-24] But, no systematic efforts were made to capture all the real-world clinical experience with genomic application yet. In general, a scoping review is considered appropriate to identify key characteristics or factors related to a specific topic.[25] Such an initiative could provide a holistic picture of the barriers to genetic testing implementation in any healthcare setting and the required resources to overcome those barriers.

Another major drawback in genetic testing implementation is the acceptance of the test among patients because of limited knowledge about genetics and its role in therapeutic response.[23] To date, most of the published studies explored the public perception of genetic testing either in specific diseases or included specific population groups.[26-29] Among these studies, a systematic review concluded that only a small proportion of the minority population is aware and knowledgeable about genetic testing for cancer risk. Although this systematic review contained a large number of US-based studies, the majority of those included at-risk patients or those already with a cancer diagnosis.[28] Therefore, the knowledge and attitudes of the racial and ethnic minority population are lacking. A recent study used Amazon MTurk US workforce and reported that African Americans were less likely to believe in genetic testing compared with White.[30] However, the study sample had a total of 56 African Americans, and the majority were slightly younger than the US general population. Another minority group that had a limited presence in the published studies is Hispanics. Persistent disparities were observed between Hispanics and non-Hispanic Whites on the overall awareness of direct-to-consumer (DTC)

genetic testing in the Health Information National Trends Survey (HINTS) from 2007 to 2014.[31] Although a high level of basic awareness was found in a Latino population, the qualitative study was conducted in a small sample of Latinos residing in New York city.[32] Therefore, the results may not be generalizable to the broader Hispanic population. More studies targeting the racial and ethnic minority population to understand their knowledge and attitudes of genetic testing are warranted. This information may help to design interventions targeting these populations to increase the uptake of genetic testing.

Besides, the shifting of genetics to genomics is unavoidable, and the first two decades of the 21st century have been considered as a historical era to witness this great transition.[33] With the rapid development of this field, newer terms such as preemptive testing, reactive testing, whole-genome sequencing, whole-exome sequencing, and next genome sequencing have been introduced in the last decade. While examining the attitudes and perceptions towards genetic testing, previous studies that are mentioned above mostly focused on overall genetic testing, DTC genetic testing, genetic testing for disease risk, genetic testing for hereditary conditions or ancestry, and genetic testing to guide treatment, etc. No study ever examined the perception towards preemptive vs. reactive testing, multi-gene panels, genome-wide sequencing, and other multi-genic tests for disease diagnosis, prognosis, and treatment. Further, current evidence-based, peer-reviewed guidelines are required to facilitate the adoption of genomic testing into clinical practice. Several platforms, such as Clinical Pharmacogenetics Implementation Consortium (CPIC), Pharmacogenomics Knowledge Base (PharmGKB), and the Dutch Pharmacogenetics Working group (DPWG), have been publishing pharmacogenomic literature every year.[34-36] Along with this continuous expansion of pharmacogenetic knowledge and evidence, advanced sequencing technology, the ability to read genomic data, and improved

analysis techniques were observed in the last two decades.[37] Patients' knowledge and attitudes toward genetic testing can also be driven by all these factors.

Genetic testing is thriving, and its impact on human lives is enormous. However, the slow uptake of genetic testing into routine clinical practice indicates that much remains to be explored with regards to finding the best ways to facilitate the implementation process. Therefore, this study seeks to address the gap in the current literature.

1.2 Overall Objective

The overall objective of this dissertation project was to address this question, "What are the ways to facilitate genetic testing uptake among people living in the US?" This was accomplished by addressing three major areas: 1) examining the geographic access to genetic testing center using road network analysis i.e., closest facility analysis, 2) synthesizing current evidence to identify barriers and facilitators for implementation of genetic testing in a healthcare setting using a scoping review, and 3) identifying gaps in genetic testing awareness and perceptions through a national online survey of the US general public, focusing on different racial/ethnic populations and people residing in rural and urban areas. Hence, we used the following three aims:

1.3 Specific Aims

1.3.1 Aim 1. To examine the geographical access to genetic testing centers for people living in the United States.

The objective of this aim was to calculate the travel time to the nearest genetic testing center from each census tract and to examine the key differences in demographic characteristics between people living in different travel time categories including less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes, and 180 minutes and above. We obtained the genetic testing center addresses from the American College of Medical Genetics and Genomics (ACMG) and geocoded the genetic testing center locations as *destinations* using ArcGIS address locator. We calculated the centroid points for each US census tracts and set them as *origins*. We then performed a road network analysis of travel times between origin and destination using closest network facility analysis feature in ArcGIS online ready-to-use services. To address racial disparity, we also accounted for race and ethnicity (i.e., White, Black, Asian, and Hispanic etc.) using the US Census data 2020 and performed subgroup analysis as required.

1.3.2 Aim 2. A scoping review to synthesize current evidence on the barriers and facilitators to implementation of pharmacogenetic testing in a healthcare setting.

We conducted a scoping review with an expanded literature search using Ovid MEDLINE, Web of Science, International Pharmaceutical Abstract (IPA), and Google Scholar to look for any studies reporting implementation of pharmacogenetic testing in a healthcare setting, from a health systems perspective. To date, there has been no scoping review on the real-world experiences of pharmacogenetic testing implementation. We reported the barriers and facilitators

to implement pharmacogenetic testing in different healthcare settings using the Consolidated Framework for Implementation Science (CFIR) as a framework. Challenges, lessons learned, and resources to aid the pharmacogenetic implementation process were discussed in detail. The synthesized evidence will act as a checklist of potential barriers and their solutions for healthcare settings that are interested in implementing or expanding pharmacogenetic service in future.

1.3.3 Aim 3. To assess the awareness, perceptions, and preferences toward genetic testing among the United States general public, and how this may vary by racial-ethnic group and rural-urban status.

The objective of this aim was to conduct a cross-sectional online survey among populations residing in the US including different racial-ethnic groups and rural-urban groups to understand their awareness, perceptions, and preferences about genetic testing. We used a Qualtrics panel to recruit a total of 1,600 members of the general US population. The Theory of Planned Behavior (TPB) was used to develop the perception survey items and scales using the attitude, perceived behavioral control, subjective norm, and intention constructs. The survey results also examined the literacy and numeracy levels of the survey respondents. We investigated public perceptions towards genetic testing (e.g., genetic testing for disease risk assessment, drug selection, and dosing) in different health conditions. Findings were compared among different racial-ethnic and rurality subgroups.

1.4 Innovation and Impact

This study was innovative in three important aspects. First, this was the first study to calculate the travel time to the nearest genetic testing center from each of the census tract and examine geographical access to the genetic testing center among racial-ethnic groups. This will largely help researchers and policymakers to address racial disparities in access to genetic testing centers. Second, no published scoping review on the real-world experiences of pharmacogenetic implementation processes including barriers and facilitators to implement has been identified. Although there are articles providing guidelines to follow during implementation, most of these were either individual or institutional perspectives. The current evidence synthesis is beneficial to understand the different barriers and facilitators experienced by the early implementers. Lastly, only a few previous studies included racial and ethnic minority populations while examining the attitudes and perceptions toward pharmacogenetic testing and often had a very small sample size. This study largely focused on the perceptions, awareness, and preferences towards genetic testing among different racial and ethnic populations, including African Americans, Asians, and Hispanics, and compared the results with non-Hispanic Whites.

This study is impactful in three ways. First, this study examined the key differences in racial and ethnic characteristics between people living in different travel time categories such as less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes, and 180 minutes and above. Second, the scoping review identified key facilitators and barriers of genetic testing implementation in routine clinical care in both US and international settings. These key factors can be used to help healthcare settings plan when they offer genetic testing services. Survey respondents' demographic information was collected to examine the association between the different demographic characteristics and awareness, perception, and preferences toward genetic

testing concepts as well as different types of genetic testing strategies. Finally, this study intentionally included a large number of racial and ethnic minorities as well as rural residents in the online Qualtrics survey.

Overall, this study provided a comprehensive analysis regarding access to genetic testing centers, implementation issues, and public awareness, perceptions, and preferences towards genetic testing concepts and strategies involving large minority groups as well as rural populations. Using this study findings, we were able to provide recommendations to overcome the barriers in accessing genetic testing facilities, ways to increase the extent of implementation in routine clinical care, and ultimately increase awareness among underserved populations.

Chapter Two

Literature Review

2.1 Introduction

Since the mapping of human genome 18 years ago, genetic testing has become the staircase to the future of medicine.[38] The huge impact of genetic assessment led the National Institutes of Health (NIH) to allocate millions of dollars in a national effort, the All of Us Research program, to collect specimens from a million people across the US to identify individual variation in genes, environment, and lifestyle.[39] The ultimate goal of this initiative is to attain the ability to treat each patient individually based on their genetic makeup and achieve the best health outcome. The NIH Precision Medicine Initiative (PMI) Working Group strongly recommended to include diverse social, racial or ethnic, and ancestral populations living in different geographic, and socioeconomic circumstances in their one-million cohort.[40] However, these different underrepresented population groups including racial or ethnic minorities face multiple barriers to get involved in biomedical research.[41] Therefore, the main objective of this study is to focus on the barriers such as geographic accessibility, implementation, perception, awareness, and attitude toward genetic testing to better understand and tackle disparities in precision medicine. In order to set a foundation for this study, the following sections in this chapter will review the genetic terminologies, current genetic testing status in the US, overall and geographic access to healthcare, and available genetic testing locations in the US. Later, we will discuss genetic testing implementation stages, current status, and the importance of clinical decision support tools. Literature on the acceptance of genetic testing among the US population, with a particular focus on underrepresented population groups, will be summarized. Lastly,

theoretical frameworks will be discussed, especially the CFIR and the TPB, to support and build the methodological plan of this study.

2.2 Genetic Terminologies Used in this Work

Defining multiple terms such as gene, genomics, genotype, phenotype, pharmacogenetics, pharmacogenomics, whole genome sequencing, next generation sequencing, preemptive testing, and reactive testing in advance is useful to describe specific technical aspects of genetic testing and precision medicine. A set of definitions are provided below to facilitate use of clear terminology. According to the CDC, gene, a key substantial unit of heredity, is a part of DNA that contains information required to build a protein.[42] The NCI defined genomics as *"the study of the complete set of DNA including all of its genes in a person or other organism*".[43] As a human being, we have many common DNAs, but as expected, large number of variations are also observed among individuals. While genotype refers to the specific form of a DNA sequence that a person or organism has, phenotype is defined as a person's physical and behavioral traits such as hair color, eye color, height, cognitive pattern, and personality which are influenced by both genotypes and environment.[44-46]

Pharmacogenetics is the study of variability in drug responses because of a person's genetic makeup.[47] Although used interchangeably, PharmGKB identified "pharmacogenetics" as the effect of a single gene on the response to a single drug and indicated "pharmacogenomics" as a much broader term which determines how all the genes, or the genome has an effect on the drug responses.[48] There are different types of genetic testing. For example, single-gene tests use only one gene while panel testing includes a group of genes in one single test.[49] Another testing process which determines all the nucleotides of a person's complete DNA sequence and non-

coding sequence is called whole genome sequencing (WGS).[50] Next generation sequencing (NGS), also known as massively parallel or deep sequencing, is a high-throughput sequencing technology of millions of small fragments of DNA running alongside.[51] Preemptive testing suggests that patient will be taking the test before the disease evolves and medication is prescribed.[52] However, in reactive testing, patient will take the test after the disease is identified and medication is prescribed but the treatment is started.[52]

2.3 Current Genetic Testing Status in the United States

According to the Fortune Business Insights analysis, the US genetic testing market is estimated to become more than a 10-billion-dollar industry by 2027.[53] In general, conventional genetic testing is guided by a healthcare provider in a clinical or biomedical research setting. However, a huge increase in direct-to-consumer (DTC) testing has been observed in the past decade, with the potential to become even a more mainstream testing platform in the future.[54,55] DTC tests are marketed directly to the consumers without any guidance from a healthcare provider or involving the health insurance company in the process.[56] The DTC tests usually do not sequence the whole genome and mostly provides polygenic risk scores, genotype at a specific point, carrier screening, and uninterpreted raw genetic data.[57] The majority of these tests use SNP-chip genotyping to track specific variants throughout the genetic code.[57] Although DTC testing provides opportunities for consumers to better understand the importance of precision medicine, previous studies have discussed the limitations of DTC genetic tests such as false positives, low predictive value, inconclusive results, use of limited genetic variants, stress related to unexpected test results, and lack of scientific evidence.[56,57] The American College of Medical Genetics and Genomics (ACMG) strongly recommends use of conventional genetic testing over

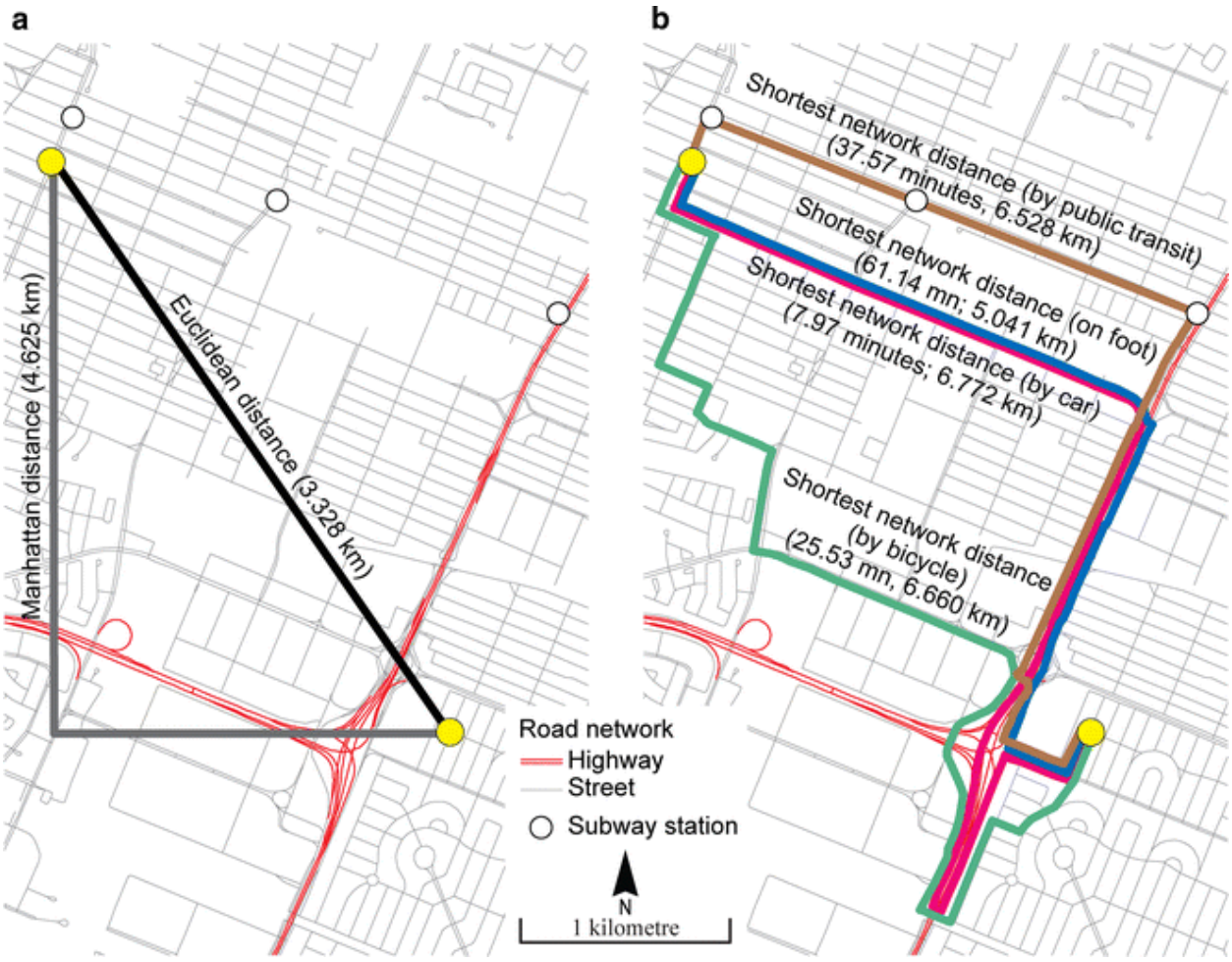
DTC testing because of its appropriate use of laboratory procedures and inspection from a validated agency.[58] Nonetheless, with the progress of advanced sequencing technology, the cost to take a genetic test has decreased significantly. Currently, genetic test costs around $100 to $2,000 in the US based on the type and complexity of the testing procedure.[59]

2.4 Access to Healthcare

Access to care is an important dimension in determining overall population health. There is no single definition that can characterize the word "access" and therefore, multiple definitions are found in the literatures. Parker et al., defined access as "the ability to reach, obtain, and afford entrance to services".[60] Penchansky and Thomas proposed a taxonomic definition of access to fit between the patient and healthcare access that includes five broad dimensions (availability, accessibility, accommodation, affordability, and acceptability) for which operational measures can be developed.[61] Gulliford et al. discussed four dimensions of access: service availability, utilization of services and barriers to access, relevance, effectiveness and access, and equity and access.[62] The Agency for Healthcare Research and Quality (AHRQ) defined access to health care as "the timely use of personal health services to achieve the best health outcomes" and mentioned coverage, services, timeliness, and workforce as four key components of access to health care.[63] In all of these definitions, several dimensions (i.e., ability to reach, accessibility, service availability, and coverage) are spatial in nature. Spatial accessibility identifies which residents of a given geographic area can reach different types of facilities.[64] There are different ways to measure spatial accessibility such as distance to the facility, number of services within a specific distance or specific time, mean distance to n closest facilities, gravity models, and two-step floating catchment area methods.[65-69] In general, distance

is the most commonly used measure of spatial accessibility and there are two major types of distance measures, cartesian and network distances.[70] A figure has been adopted from Apparicio et al. to clearly demonstrate the difference between cartesian and network distances.

Figure 1: Types of distance. a. Cartesian distances. b. Network distances (Adopted from Apparicio et al 2017)[70]



2.4.1 How access to care is related to health outcomes?

It is already apparent that geography is not just a map, it has much larger meaning in determining geographical access to healthcare and eventually has an impact on health outcomes.[71] Geographic variables such as distance to care, travel time, and having a driver's license were associated with regular check-up, and in some cases, with chronic care visits too.[72] Previous studies showed that longer distance to healthcare was associated with a lower healthcare use.[73,74] In another study, children with type 1 diabetes had significantly higher HbA1C values and lower satisfaction if they had to drive more than 2 hours compared with those who drove less than 60 minutes.[75] The majority of the included studies in a large systematic review (83 out of 108 studies) found that there is a negative correlation between distance or travel time to healthcare and health outcomes, suggesting individuals living closer to the facility will have better health outcomes compared to those who lived further away.[76] More than a quarter of the included studies used straight line distance as the measurement while the remainder used travel time or road network-based distance, mostly utilizing GIS software. No consensus was found on how the travel distances or travel times should be categorized with different studies using different measures. However, travel times greater than 4 hours one way could be unreasonable to many individuals because even an entire day seems inadequate to take the test and spend 8 hours on the road. Therefore, several studies used 3 hours to reflect a feasible limit of a one-way trip to a healthcare center, receive the service, and return to home in a day.[15,77-80] The majority of the included studies assumed that individuals would travel by car.[76] A travel survey found that around 87% of patients used a car to go to the hospital.[81] Although it is important to understand how everyone is travelling, selecting the appropriate mode of transport would be difficult for different communities or large populations. Overall, it is imperative to

include distance or travel time as a measure to indicate whether individuals have access to healthcare facilities. Successful characterization of travel time to healthcare can help communities to identify available resources as well as assist policymakers in allocating resources to improve overall health.[82]

2.4.2 Disparities in access to healthcare

Around 60 million people, roughly one-fifth of the total US population, lived in rural areas according to the 2010 Decennial Census Data.[83] Since rural areas tend to have a high poverty level, transportation is a major limitation for many patients to receive proper health care.[84] Historically, spatial arrangement of people, distribution of facilities, and the spatial networks of transportation have been the key factors in determining geographic accessibility of health care services as well as addressing disparities.[67,85] Previous studies suggest that primary care services are not uniformly distributed across the US.[86] For example, different neighborhoods had different spatial accessibility of primary care in Philadelphia with higher percentages of minority populated areas having less spatial accessibility.[87] According to the pew research organization, rural residents must travel an average of 10.5 miles to go to the nearest hospital while urban residents cover only 4.4 miles on average.[88] Rural residents in the Deep south had to travel greater distances to receive treatment for prostate, breast, and colorectal cancer compared with the urban populations.[89] According to Healthy People 2020, expanding access to health services would also help in reducing health disparities.[90]

2.4.3 Available Genetic Testing Facilities/Locations in the United States

There are two primary sources to find available genetic testing facilities in the US. A total of 241 human gene testing laboratories were found to be located in the US based on the Genetic Testing Registry (GTR) database.[91] For each of these laboratories, several attributes such as GTR lab ID, geographic location information, contact information, list of services, conditions and tests, list of certifications and licenses were provided on the website. The American College of Medical Genetics and Genomics (ACMG) is an alternative source where a list of 1,292 physical locations for genetic clinics across the US is provided.[92] There are 14 genetic clinics that do not have any physical location.[92] The GTR does not independently verify the information submitted to them. On the other hand, the ACMG reviews the information and has an approval process. However, the approval procedure is not well-described on the website. None of them makes any endorsements for any tests or laboratories and does not warrant the quality of the services provided. The major difference between these two sources is that the first one focused on the laboratories where the genetic testing are done, all or some portions, while the other source listed all the different healthcare settings that offered different genetic services.[93] In another words, the ACMG physical locations provides genetic services such as collecting the samples, sharing the results, and providing genetic counseling and expertise, but the testing may not be done in that specific location.

2.5 Genetic Testing Implementation in the United States

Nearly 75,000 genetic tests were found to be available on the market in 2017 based on two different sources: 1) test catalog database which tracks existing and new tests marketed by CLIA-certified laboratories, and 2) genetic testing claims database that included 1.7 million

commercial payer claims.[94] Around 86% of them were single-gene tests, and most strikingly, less than 5% of the total spending was accounted by pharmacogenetic tests. In another study using IQVIA managed care population data from 2013 to 2017, the number of patients receiving at least one pharmacogenetic test out of the 6 most common single-gene tests (CYP2C19, CYP2D6, CYP2C9, HLA1, VKORC1, and UGT1A1) ranged from 733 to 1567 per year.[95] Although there are numerous possibilities to receive genetic testing outside of managed care systems, the calculated number of tests per year is considered low given that a large population (~11 million) were included in the study. Because of the lack of implementation in real-world settings and a paucity of real-world evidence, previous studies have suggested using alternative sources and study designs to bring forward more evidence to support clinical implementation of pharmacogenetic testing.[96]

2.5.1 Essentials in Genetic Testing Implementation

With the abundance of genomic information, it is essential to promptly translate this technology into clinical practice promptly.[97] Large network groups such as the Implementing Genomics in Practice (IGNITE) network surveyed four primary stakeholders (i.e., patients, health care providers, payers, and governmental organizations) and identified seven key drivers to implement a sustainable genomic medicine program.[98] These key drivers were infrastructure, clinical evidence or effectiveness, economic measures, workforce impact, education, regulatory issues, and research and development. Numerous literature reviews that have been published in the last 15 years, with most discussing the implementation process in different settings and different population groups, providing an overview of some implementation initiatives and institutes, compiling the benefits of pharmacogenetic testing using different clinical outcomes,

identifying barriers, and useful strategies to overcome challenges.[17,99-112] Although these articles have presented adequate information to facilitate the implementation of pharmacogenetic testing in routine clinical care, all of these reviews were from either an individual or institutional perspective and did not follow any systematic search strategy. Therefore, it is unknown to what extent these reviews included the available literature and how those included articles were chosen. Often, these reviews are not reproducible because there is no specific methodology involved in conducting the review. In addition, some of these reviews were focused on specific genotypes, drugs, or diseases and synthesized implementation evidence only for that specific topic.[99,102,106,108,112] Besides, it was not clear whether genetic testing implementation in US healthcare settings is different than other countries.

2.5.2 Knowledge Gaps in Genetic Testing Implementation

Aside from these reviews, a large systematic review of 283 articles identified several gaps in genomic medicine implementation in 2019.[3] Only a few included studies incorporated implementation science framework to guide their research and did not describe the contextual factors appropriately. Also, there is a lack of evidence-based implementation strategies because current data are mostly observational in nature instead of randomized controlled trials. Although the review attempted to describe the current state of implementation science in genomic medicine, there were several limitations in this study. First, this study used Public Health Genomics and Precision Health Knowledge Base (PHGKB) maintained by the CDC which primarily uses PubMed database only. To ensure maximum coverage, it is recommended to use a combination of databases for conducting a systematic review.[113] Second, this review included articles that were not considered as implementation studies. Third, the review focused on all of

the translational research phase (T2 to T4), from bench to bedside. Therefore, the objective was not to synthesize evidence for implementation in routine clinical care only, rather it included studies about dissemination research, efficacy studies investigating whether it works under optimal conditions, and lastly the implementation studies. Lastly, no information regarding the type of clinical settings that are implementing genetic testing, their characteristics, types of genetic tests, use of clinical decision support tools, real-world experiences, challenges, and lessons learned were provided in this systematic as these important factors were out of scope of that systematic review.

There are a few exemplary articles that focused on the requirements to implement a pharmacogenetic testing program in a clinical setting. Owusu Obeng et al. published an article in 2021 outlining the preparatory steps including selection of medications, genes, and the laboratory for testing, target patient population, multidisciplinary implementation team, resources for implementation, and other clinical considerations which are instrumental to implement a pharmacogenetic program in clinical practice.[114] Another review also discussed several important factors such as ordering tests (e.g., single or panel), results interpretation, understanding metabolic consequences, drug-drug interactions, and training in the implementation of pharmacogenomics in clinical practice.[115] Weitzel et al. illustrated a four step process including patient identification, pharmacogenetic test ordering, application of pharmacogenetic test results, and patient education to successfully implement pharmacogenetic testing in a primary care setting.[116] Although these articles provide important information on the prerequisites of implementation and can be followed as a guideline, a comprehensive view on the current status of pharmacogenetics implementation, real-world experiences, challenges faced, and lessons learned from the clinical practice sites is missing.

2.5.3 Clinical Decision Support Tool

One of the major barriers in implementing precision medicine in routine clinical practice is that there is a need for new informatics tools and optimized clinical workflows.[117] Clinical decision support tools, that are usually incorporated into electronic health records (EHR) or medication dispensing software, are known to optimize clinical workflow and facilitate the implementation of personalized medicine.[118,119] According to the Agency for Healthcare Research and Quality (AHRQ), clinical decision support tools can help make decisions about health care such as providing possible treatment choices, reminders for preventive care, and alerts about potentially dangerous contraindications to the clinicians, patients, and others.[120] The Center for Disease Control and Prevention (CDC) defines CDS tool as computer-based programs that are incorporated within the electronic health record (EHR) to provide timely information to help the healthcare professional to make decisions about patient's care using evidence-based clinical guidelines.[121] Sutton et al. provided an overview on the use of CDS tools and prepared a list of benefits, potential harms, and evidence-based mitigation strategies.[122] More than two-thirds of randomized controlled trials found that decision support systems significantly improved clinical practice in a large systematic review.[123] Overall, CDS tool provides enormous support to healthcare providers and eventually ensures the quality of care.[122] Integrating pharmacogenomic information in the EHR is an indispensable part of precision medicine, and CDS can easily facilitate this integration.[124] Although the benefits and limitations of CDS system are established, it is unknown to what extent it is being used during the genetic testing implementation in real-world settings.

2.6 Acceptance of Genetic Testing among the US population

Knowledge and belief about the intervention is an important element in facilitating genetic testing implementation process in routine clinical care.[125] A survey among general public in North Carolina found higher knowledge levels exist among the general public about genetic testing while differences in knowledge scores were observed among racial groups.[26] However, most of the participants were young and highly educated. Positive attitudes toward genetics and genetic testing were observed in three Jackson and Framingham heart cohorts.[126] Although the results were published in 2019, this study collected the data in 2011-2012. Hence, it is unknown whether the findings are applicable to present time given that genetics has changed extensively over the last 10 years. Additionally, the participants had already consented to participate in the genetic testing. Thus, it is expected that they would have positive attitudes toward genetic testing. In another study, around 60% of US adults reported to have at least some interest towards whole genome testing.[127] However, whole genome sequencing was introduced to the study participants briefly before the questions were asked. Therefore, it is unknown to what extent the participants had an actual baseline understanding about this whole genome testing. Also, important confounders such as sex, health literacy, and previous exposure to genetic testing were missing in this study. Additional literature regarding perception, awareness, and preferences toward genetic testing can be divided into these three sections below.

2.6.1 Health Information National Trends Survey (HINTS)

The Health Information National Trends Survey (HINTS) routinely collects data about public knowledge of, attitude towards, and use of cancer and other health related information in a nationally representative sample involving adults 18 years and older.[128] This survey collects

information about genetic testing attitudes and privacy as well. These genetic testing related questions (i.e., which of the following types of genetic tests have you heard of, from which sources, have you ever had any genetic tests, who did you share results with, who helped you understand the results, how much do you think genetics determine whether a person develops diabetes/obesity/heart disease/cancer, how much would you want to know if you have a genetic change that increases your chances of getting cancer, how important is knowing a person's genetic information for preventing/detecting/treating cancer etc.) are available from the 2011 HINTS to 2020 HINTS. Around 43% of the respondents in the 2017 HINTS survey were not aware of genetic tests for health.[129] Even a higher percentage of respondents were unfamiliar with genetic testing for specific reasons such as treatment choice or drug efficacy.[129] Several previous studies focused on DTC genetic testing utilizing the HINTS database and reported that minorities were significantly less aware of DTC genetic testing compared to non-Hispanic Whites, even after controlling for essential covariates such as age, education, gender, income, marital status, family history, information seeking behavior, and most importantly, the gaps are still widening.[31,130,131] Besides, health literacy measurement in the HINTS survey was a general estimation instead of a validated instrument. Although 2013 HINTS did include the Newest Vital Sign, a validated instrument for health literacy, it was not included in the later rounds. As DTC genetic testing is not considered as an alternative for genetic testing in disease risk assessment, disease prevention, diagnosis, and treatment choice, awareness of DTC does not necessarily imply the awareness of genetic testing for the abovementioned reasons.[131]

2.6.2 Underserved Population - Racial and Ethnic Minorities

A recent systematic review on racial and ethnic differences in knowledge and attitudes about genetic testing included only 12 studies conducted in the US across 20 years and found that minorities were consistently less aware, less knowledgeable, and more concerned about genetic testing in general compared with Whites.[132] One reason for such lower attitudes toward genetic testing could be because of lack of adequate information about genetic testing provided by the physicians treating minorities. Besides, minority serving physicians were less likely to use genetic testing.[133,134] Nonetheless, there were several limitations and research gaps highlighted by the review authors.[132] First, there was limited literature focusing on racial/ethnic differences in knowledge and attitudes towards genetic testing. Second, this review did not compare the differences in knowledge and attitudes based on important socioeconomic factors because only a few studies included demographic factors such as income or educational attainment. Third, subgroup comparisons were also not available because of small sample size issues. Fourth, none of the included studies investigated attitudes toward pharmacogenetic testing. Overall, the authors suggested a need for future studies to include racial/ethnic subgroups to examine whether disparities exist over time. Another large systematic review on awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups included a total of 39 studies conducted in the US.[28] Results were similar to the previous notion that minorities were less aware of genetic testing compared with Whites. However, the majority of included studies recruited either at-risk patients or patients with a cancer diagnosis, thus were not able to represent the general population of minorities.

Surprisingly, another systematic review of both qualitative and quantitative studies reported that there was no association between likelihood to participate in genetic research and

race/ethnic minority group.[135] Most included studies had limitations such as questionable definition or groupings of different races and ethnicities, and inadequate reporting of demographic characteristics. In addition, the intention to participate in genetic research does not suggest that minorities were aware of different types of genetic testing. Only one study in that review examined the association between knowledge about genetic testing in Alzheimer's disease and race/ethnic groups and found that Blacks were less knowledgeable than Whites.[136] Another recent semi-structured interview with 20 Latino women supported the notion that Latinos have limited awareness about genetic testing services and is multifactorial.[137] These data suggest that there are significant differences in awareness, knowledge, perception, and attitudes towards genetic testing between non-Hispanic Whites and minorities.

2.6.3 Underserved Population - Rural Residents

In the US, rural residents had a lower awareness of direct-to-consumer genetic testing compared to urban residents, according to a nationally representative sample.[131] In contrast, another survey among three rural Illinois communities reported more than two thirds of the survey participants were aware of genetic testing for cancer and other diseases.[138] Another study with only three communities and a small sample size reported that rural community members were knowledgeable regarding different genetic testing.[139] Similarly, a small-scale study involving rural residents also found that participants had positive attitudes toward pharmacogenomics.[140] But the study did not have access to the participants' demographic information. On the other hand, there were no significant differences between rural and urban Oregon residents in self-reported genetic testing knowledge.[141] Overall, all of these studies

included rural population from a few specific communities and may not be representative of the entire US rural population.

2.7 Genetics and Genomics Are Changing Every Day

With the fast-growing genomic knowledge, humans have access to advanced technologies and information about their genes to guide individual care. However, the relationship between genomics and diseases is multifactorial which requires a trained population to understand the interactions.[142] Although lay people may have a better understanding regarding genetic testing in hereditary conditions and ancestry, it may become bewildering to them when genomics moves into medicine.[142] According to a large survey among an adult population in New York, as age increases, genetic knowledge tends to decrease.[143] One possible reason for this could be that young people are usually more up to date with new knowledge and trends. Thus, it becomes difficult for the general public to keep track of newer genetic information as they grow older. Previous studies rarely focused on patient knowledge and attitude towards this evolving nature of genomics. For example, a recent qualitative study investigated US payers' knowledge, awareness, and perspectives on preemptive pharmacogenetic testing.[144] However, similar studies examining the patient knowledge regarding specific types of genetic testing are not available. Therefore, to what extent the US general public are familiar with the newer genomic terms and procedures is unknown.

2.8 Theoretical Frameworks

Theoretical frameworks are instrumental to any types of research methods and should be included in the research study to frame and justify the importance and significance of the work.[145] In this study, two well-known theoretical frameworks, CFIR and TPB, are used in aim 2 and aim 3, respectively. In light of the genetic testing, these frameworks are dsescribed below along with necessary tables and figures.

2.8.1 Consolidated Framework for Implementation Research (CFIR)

The Consolidated Framework for Implementation Research (CFIR) consists of a total of 39 constructs within five major general domains including intervention characteristics, inner setting, outer setting, characteristics of individuals, and process (Table 1). Previous studies highly recommended incorporating implementation science theoretical frameworks in genomic medicine.[146] One of the biggest networking group, Implementing Genetics in Practice (IGNITE), applied the CFIR guide in their evaluation process and identified a set of important constructs specifically for genomic medicine implementation.[125] A recent systematic review on familial hypercholesterolemia used CFIR to identify the barriers and facilitators to genetic testing.[147] Since this study aims to synthesize evidence on the challenges and solutions to aid genetic testing implementation in routine clinical care, this study adopted the CFIR constructs as a structural guide to report the findings of the proposed scoping review. A brief description of all these CFIR constructs is discussed in the next section.[148]

Complexity refers to the perceived difficulty of the genetic testing that includes centrality, disruptiveness, duration, intricacy, number of steps required to implement, radicalness, and scope

of implementation. Relative advantage deals with the stakeholders perception of the implementation advantages over the possible alternative solution. Genetic testing will have desired outcomes and stakeholders perception of the evidence supporting such belief defines the evidence strength and quality construct. Trialability confirms the ability to implement genetic testing on a small scale while adaptability ensures whether the genetic testing implementation can be tailored to meet the local needs. Design quality and packaging is critical to implementation success because imperfect design or packaging will bring negative attitude towards the genetic testing procedures. Genetic testing facilities can be internally developed or may be provided by an external entity. The stakeholders should have clear perceptions regarding the source of the genetic testing procedures to facilitate an effective implementation. Active network and positive communication across the organization positively influence implementation. Norms and values shape the culture of an organization which ultimately defines the behavior of an organization towards the genetic testing implementation. The size of an organization, age, and experience in the healthcare sector determines the structure of the organization. Readiness for implementation includes leadership engagement (i.e., commitment, involvement, and accountability of the leaders), available resources (i.e., money, educational training, and time), and access to knowledge or information. Several characteristics represent implementation climate such as tension for change, degree of tangible fit or compatibility, importance of the genetic testing withing the organization or relative priority, organizational incentives and rewards, goals and feedback, and climate of micro-environments related to the implementation. Constructs included in the outer settings such as external policies and incentives, peer pressure, and patient needs, and resources are self-explanatory. Cosmopolitanism, the other construct from outer settings, indicates the organizations relationship

with other external entities. Individuals stage of change could be introduced with an underlying model (i.e., Prochaska's trans-theoretical model) as an important measure of implementation progress while the identification with organizational constructs refers to how individuals perceive their relationship with the current organization. Individuals knowledge and beliefs about the genetic testing, belief in their own capabilities, and other personal traits including intellectual ability, learning style, values, and competence are key parts of the characteristics of individuals domain. Process, the single most difficult domain in implementation research, consists of four well-known constructs such as planning, engaging, executing, reflecting and evaluating and are routinely common across organizational change models.

Table 1: Consolidated Framework for Implementation Research (CFIR) Domains and Constructs

Domains	Constructs
Intervention Characteristics	Complexity Relative advantage Evidence strength and quality Trialability Adaptability Cost Design quality and packaging Intervention source
Inner Setting	Networks and communications Readiness for implementation • Leadership engagement • Available sources • Access to knowledge/information Implementation climate • Tension for change • Compatibility • Relative priority • Organizational incentives and rewards • Goals/feedback • Learning climate Culture Structural characteristics

Outer Setting	External policy/incentives Peer pressure Patient needs/resources Cosmopolitanism
Characteristics of Individuals	Knowledge and beliefs about the intervention Self-efficacy Individual identification with organization Individual stage of change Other personal attributes
Process	Executing Planning Reflecting and evaluating Engaging • Opinion leaders • Formally appointed internal implementation leaders • Champions • External change agents

2.8.2 Theory of Planned Behavior (TPB)

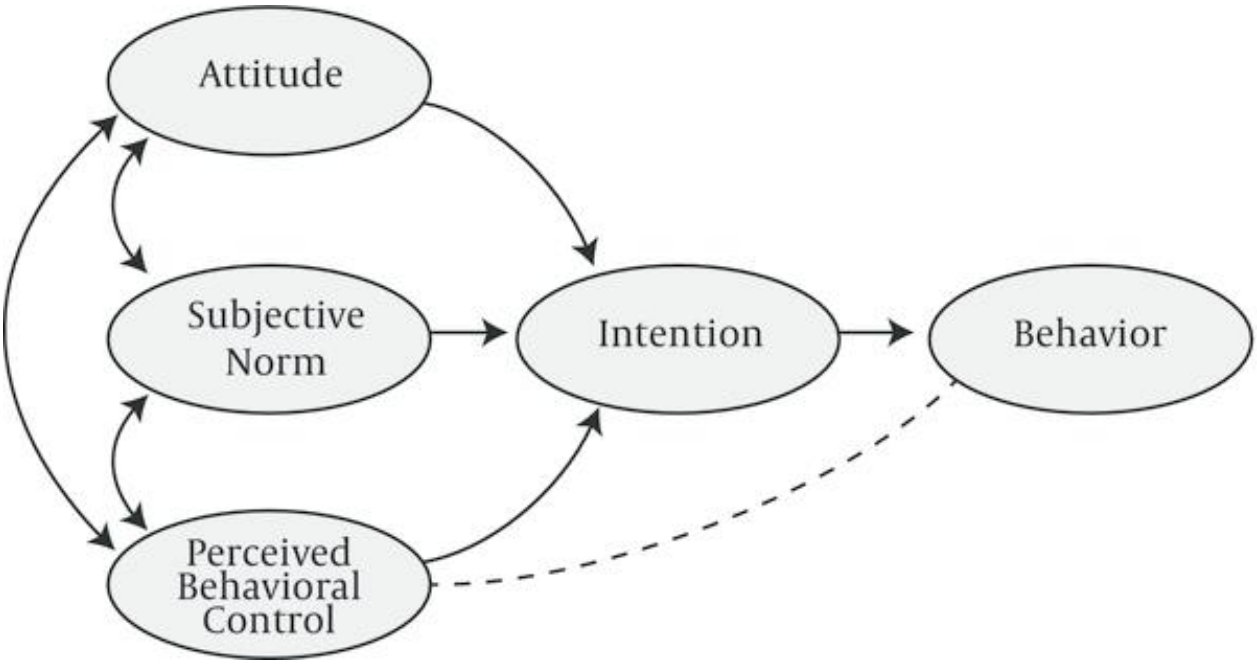
Originally, the TPB is an extension of the theory of reasoned action (TRA) proposed by Ajzen and Fishbein.[149] Attitude and subjective norm are the two prime factors that influence intention which eventually leads towards the actual behavior according to the TRA. Intention,

the willingness to engage in taking a genetic test, is the central factor in this model. The authors assumed perfect volitional control in the TRA and realized the limitations of this assumption over the years.[150] Later, perceived behavioral control was added to correct the assumption and they renamed it as TPB. The updated constructs of the TPB model are presented in Figure 2. Attitude is defined as whether a person has a positive or negative perspective towards taking the genetic test. Subjective norm emphasizes whether most people would support or disapprove taking the genetic test. Lastly, perceived behavior control suggests that people may easily perform the genetic test due to control over the situation or face difficulties in taking it due to lack of control.

TPB has been widely used in predicting patterns of behavior change associated with different types of health screening tests and procedures in different healthcare settings and populations.[151-159] Previous studies also adopted this theory to support genetics in healthcare.[160-162] A survey among UK adults in early 2000 found that attitude and subjective norms were the strongest predictors of intention to take genetic testing for hereditary cancer.[163] Another large study among Norwegians in late 2000 also reported both attitude and subjective norms were significantly associated with the intention to take genetic tests.[164] Studies examining the attitude towards genetic testing using the Theory of Planned Behavior in the US settings are limited. An online survey among undergraduate students regarding genetic assessment services reported that most respondents had not heard of do-it-yourself genetic assessments.[165] However, in all these studies, perceived behavioral control did not have any significant effect on intention. The UK study only used two measures for perceived behavioral control and had low internal reliability while the other studies believed genetic testing is a one-time activity and not a difficult behavior (e.g., as compared to smoking, exercise, and unsafe sex) to control.[163] Another US-based

qualitative study incorporated TPB to examine the willingness and beliefs towards genetic testing among Black mothers in US.[166] This qualitative study recruited mothers from low-income communities and had a small sample size. A systematic review of genetic testing and lifestyle behavior change included 26 studies and highly recommends use of TPB to evaluate the genetic testing behavior change.[167] Overall, these data suggest that a large US-based survey to examine genetic testing attitudes guided by the TPB or any other social cognitive theories is lacking.

Figure 2: Theory of Planned Behavior Structural Diagram



Source: Ajzen et al., 1991[149]

2.9 Areas needing further study

In summary, several factors must be understood to facilitate the use of genetic testing in routine health care in the US: geographic access to genetic testing centers, current genetic testing implementation status and barriers hindering the implementation in clinical practice, and public

knowledge, attitude, preference, and perception towards genetic testing, especially focusing on underrepresented population groups including racial/ethnic minorities and rural populations. Ultimately, results of this study will identify the geographic disparities in access to genetic testing centers, will provide an implementation framework for genetic testing-based interventions based on real-world experiences, and will inform the general public attitudes toward different genetic testing strategies and how these vary across racial/ethnic groups and rural-urban status.

Chapter Three

Methods

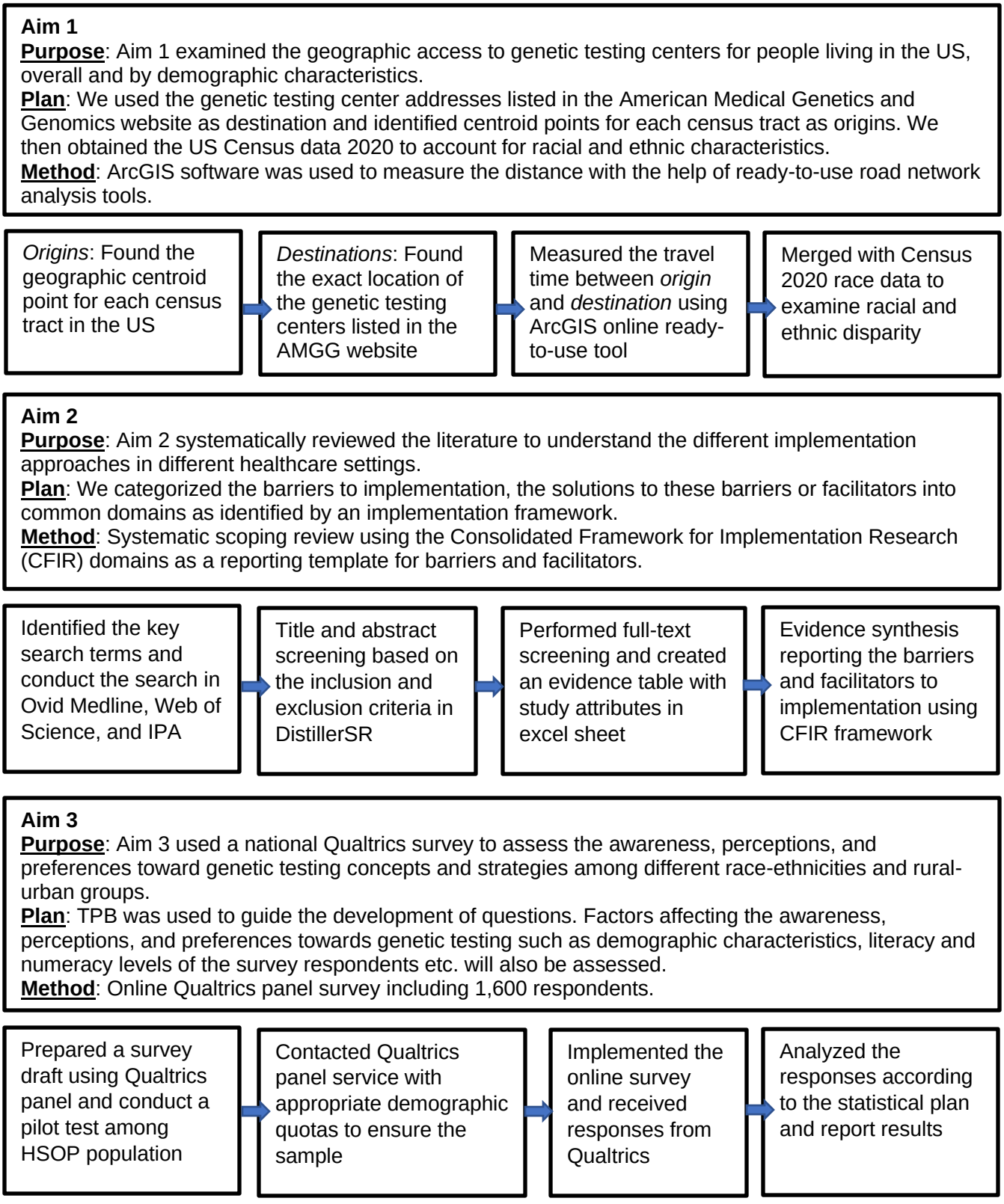
3.1 Overview

The goal of this proposed research was to identify the key factors to facilitate pharmacogenetic testing implementation in routine care. The study is composed of three specific aims. The specific aims, key research questions or domains, research designs, data collection tools, data analyses, expected findings, and limitations are provided separately for each of these three aims in section 3.2. Table 2 summarizes the questions addressed by this study and Figure 3 describes the methods.

Table 2: Questions Addressed by the Study, Relevant Aims, and Methods

Question	Aim	Method	Analysis	Anticipated Results
What is the geographical access to genetic testing centers for people living in the U.S.?	Aim 1	Road Network Analysis	Geographic closest proximity analysis with ArcGIS online ready-to-use services	Defined catchment areas for each of the listed genetic testing center and identified the number of people living within a specified distance or driving time
What are the barriers and facilitators to pharmacogenetic implementation in a healthcare setting from a health system perspective?	Aim 2	Scoping review	Narrative synthesis of different approaches to genetic testing implementation using the CFIR framework	Qualitative identification of key genetic testing implementation barriers and facilitators in the context of CFIR domains
What are the awareness, perceptions, and preferences toward different types of genetic testing strategies among different racial/ethnic population and rural-urban groups in the United States?	Aim 3	Online survey	Survey of US general population including different race-ethnicity groups and rural-urban groups in Qualtrics using TPB guidelines	Minorities and rural residents will have different level of awareness compared to Whites and urban populations, respectively. They will have differing preferences and perceptions as well.

Figure 3: Diagram of Study Methods and Rationale



3.2 Approach

***3.2.1 Specific Aim 1*: To examine the geographical access to genetic testing centers for people living in the United States.**

3.2.1.1 Research Questions:

This aim seeks to explore the following two core research questions:

- What is the travel time to the nearest genetic testing center from each census tract in the US?
- What are the key differences in racial and ethnic characteristic between people living in different travel time categories?

3.2.1.2 Research Design

This study used road network analysis to evaluate the geographical access to genetic testing center using the ArcGIS online ready-to-use service tools.

3.2.1.3 Methods

3.2.1.3.1 Study Area

This study used census tracts, usually a small and relatively permanent statistical subdivisions of a county with an average about 4000 inhabitants, as a unit of analysis. There were 85,427 census tracts defined for the 2020 census in the US and its territories excluding American Samoa, Guam, and Commonwealth of the Northern Mariana Islands.[168] A complete

map of the census tracts is presented in the appendix section. A total of 32 census tracts was excluded because no race data was available for the Virgin Islands and 614 census tracts was excluded because no population lived in those census tracts. The total resident population of the US living in those 84,781 included census tracts was found to be 334,735,155 based on the Census 2020 data.[169] A GIS layer package containing all the census tracts that represents 50 states, the District of Columbia, and Puerto Rico was readily available for the analysis using ArcGIS.

3.2.1.3.2 Data Sources – Origin and Destinations

For each census tract polygon, we calculated the X and Y coordinates using feature to point option in ArcGIS. These coordinates automatically identified the centroid point for each census tract, and each centroid point was denoted as an "origin" point in the map. We used NAD 1983 as the projected coordinate system. This commonly used projection helped us to create a map that accurately shows the distances, areas, and directions taking the spherical coordinates and transforming them to an XY coordinate system.

A list of genetic clinics in the US is available on the website of the American College of Medical Genetics and Genomics (ACMG).[92] This list was retrieved on December, 2021 which includes the geographic address, clinic type, institution, affiliation information, contact number, and regional genetics network type for 1,284 genetic clinics in total. In some cases, it also provided information regarding specialty areas (e.g., telehealth, cancer, cardiovascular, adult genetics, pediatrics, prenatal, neurogenerative, and reproductive), provider settings, counseling, telehealth, facility site type, whether Medicaid is accepted, and web address etc. We calculated the percentages of missing data for each of these facility attributes. Using the addresses and

ArcGIS online address locator, we were able to locate each of these genetic clinics on the ArcMap as a "destination" point and created a shapefile for further use. The distribution of all genetic testing centers is presented in the appendix section. The following table 3 shell was used to record the characteristics and related information from each genetic clinic.

Table 3: Summary of included genetic testing clinics

Name	Institution	Clinic Type	Address	Contact Information	Specialty Area	Medicaid	Provider Setting Type	Regional Genetics Network

The National Institute of Health (NIH) does maintain a genetic testing registry that contains list of genetic testing labs with their locations. However, this list is only focused on the testing laboratories. These are not the locations where patients must go to perform the genetic testing. In addition, this self-requested list only contains 292 testing laboratory information. Besides, the NIH genetic testing registry website provides link to ACMG clinics database for general public to navigate the clinics location. Hence, the only comprehensive list of genetic testing clinics in the US available to us was from ACMG.

3.2.1.3.4 Road Network Analysis

This study used ArcGIS ready-to-use services to find the closest facilities. The "find closest facility" tool can be found under the logistics services. The measurement unit was

selected as miles. Only 1 closest facility was selected for each of the origin or centroid points using miles as distance impedance and minutes as time impedance. We summarized the census-tract population characteristics using travel time categories such as less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes, and 180 minutes and above.

3.2.1.3.6 Feasibility

A feasibility analysis was conducted using the US county centroids as origins and 100 genetic clinic locations as destinations. We successfully ran the closest facility analysis using the ready-to-use services in the ArcMap and both geographic distances and driving times were obtained. Google Map was used to validate these driving distances and driving times.

3.2.1.4 Statistical analysis

This study used descriptive statistics to analyze both the US census tract population and genetic clinic characteristics. Driving time was used to calculate the spatial accessibility. A descriptive summary of the total US population by travel times categories i.e., less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes, and 180 minutes and above was presented. For each state, total number of the included census tracts, and the total and percentages of population they represent was calculated as well. We compared between different racial groups by different travel times using the chi-square tests, overall, each regional network, and for each state. The significance level i.e., P value was set to 0.05. This study performed all the geographical assessments in the ArcGIS (ArcMap 10.7.1, and ArcGIS Pro) and the remaining statistical analyses were conducted in SAS 9.4 software.

3.2.1.5 Expected outcomes

The expected outcomes of this aim were: 1) mapping, and characterizing population-based geographic access to genetic testing centers 2) identifying geographic extent area outside 180 minutes travel time as well as other travel time categories e.g., less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes 3) different racial subgroups were expected to have different spatial access to a genetic testing center 4) minority populations were expected to have lower access to genetic testing centers compared to Whites, respectively.

3.2.2 Specific Aim 2: **A scoping review to synthesize current evidence on the barriers and facilitators to implementation of genetic testing in a healthcare setting.**

3.2.2.1 Research Question:

This aim sought to explore the following core research question:

- What are the barriers and facilitators to pharmacogenetic testing implementation in a healthcare setting?

3.2.2.2 Research Design

This study conducted a scoping review using comprehensive search terms in different databases. We used scoping review instead of systematic review because our study goal was exploratory. In addition, it was recommended to use scoping review to identify the key factors of any intervention.[170] We also used the CFIR to guide how we classified the barriers and facilitators to genetic testing implementation reported in the literature.

3.2.2.3 Information sources

The search engines including Ovid Medline, Web of Science, and International Pharmaceutical Abstracts (IPA) were utilized to search for potentially relevant published studies from database inception point. A comprehensive search strategy was designed and implemented with the help of the current pharmacy professional librarian, Ms. Adelia Grabowsky, at Auburn University.

3.2.2.4 Methods

In this aim, a comprehensive scoping review was conducted focusing on different pharmacogenetic testing implementation approaches in different healthcare settings. All the published evidence were included based on a broad range of study designs. This study used the search terms such as “pharmacogenomics”, “pharmacogenetics”, “precision medicine”, “personalized medicine”, “implementation”, “adaptation”, “utilization”, “application”, “screen”, and “test”. In this comprehensive scoping review, full articles which are published in English language were included. The DistillerSR software was used to record all the identified articles. All the duplicate records were removed. Data screening was conducted by S.M.F. i.e., as reviewer 1 and two Pharm.D. students worked jointly as a second independent reviewer. Disagreements were resolved through discussions and consensus among the three reviewers, and further validated by another independent reviewer (C.W.A.). The following table 4 shell was used to record the characteristics and implementation related information from each potential study.

Table 4: Overall Characteristics of the Included Studies

Author (Year)	Clinical Settings Funding Information	Types of PGx Implementation	PGx Test Sample	Genes Tested	Turn-around Time	Laboratory Information Cost or Reimbursement	Barriers and Facilitators

3.2.2.5 Consolidated Framework for Implementation Research (CFIR)

The CFIR consists of five major domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and implementation process. The first domain analyzes the multi-factorial intervention characteristics and divides them into core and adaptable components. This process helps the organization to focus on the indispensable elements more closely. The next two domains address different contexts such as structural, political, cultural, economic, and social etc. to outline the composition of the settings. The fourth domain involves the individuals connected to the intervention because they are the carriers of norms, interests, and mindsets of an organization. The final domain describes the implementation process and requires an active change operation to ensure successful implementation. The overarching structure of CFIR also includes a broad array of constructs surrounding these five major domains. We used these domains as a structure to report barriers and facilitators of the implementation of genetic testing. This aim reported the barriers and facilitators of genetic testing implementation in the context of five major CFIR domains.

Figure 4: Detailed Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to August 4, 2021>

Search Strategy:

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1 Pharmacogenetics/

2 Precision Medicine/

3 (Pharmacogenomic or Pharmacogenetic or Precision Medicine or Personalized Medicine).ti,ab.

4 1 or 2 or 3

5 Implementation Science/ or Health Plan Implementation/

6 (Implement* or Adopt* or Application* or Utilization*).ti,ab.

7 5 or 6

8 4 and 7

9 Pharmacogenomic Testing/ or Genetic Testing/

10 (Screen* or Test*).ti,ab.

11 9 or 10

12 8 and 11

13 limit 12 to english language

Web of Science Results:

Set	History
# 3	#2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
# 2	((AB=((Pharmacogenomic OR Pharmacogenetic OR "Precision Medicine" OR "Personalized Medicine") AND (Screen* OR Test*) AND (Implement* OR Adopt* OR Application* OR Utilization*)))) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
# 1	((TI=((Pharmacogenomic OR Pharmacogenetic OR "Precision Medicine" OR "Personalized Medicine") AND (Screen* OR Test*) AND (Implement* OR Adopt* OR Application* OR Utilization*)))) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*

International Pharmaceutical Abstracts Results:

Database: International Pharmaceutical Abstracts <1970 to August 2021>

Search Strategy:

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1 ((Pharmacogenomic* or Pharmacogenetic* or Precision medicine or Personalized medicine) and (Screen* or Test*) and (Implement* or Adopt* or Application* or Utilization*)).ab.

2 ((Pharmacogenomic* or Pharmacogenetic* or Precision medicine or Personalized medicine) and (Screen* or Test*) and (Implement* or Adopt* or Application* or Utilization*)).ti.

3 1 or 2

4 limit 3 to english language

Google Scholar Search Strategy (first 10 pages): ((Pharmacogenomic | Pharmacogenetic | "Precision Medicine" | "Personalized Medicine") (Screen* | Test*) (Implement* | Evaluat* | Applicat*))

3.2.2.7 Expected outcomes

In this aim, all published literature, providing pharmacogenetic implementation procedure information and experiences were expected to be identified and recorded systematically. We attempted to list the barriers and facilitators to pharmacogenetic testing implementation using the CFIR domains and constructs. We aimed to discuss the challenges faced by the organizations or settings that already implemented the pharmacogenetic testing and will shed light on the solutions to these barriers. Overall, this study results are expected to identify improvements required for pharmacogenetic testing implementation strategies. Additionally, findings from this study will act as a checklist i.e., potential barriers and their solutions for the pharmacogenetic testing implementation process using the rich qualitative data found in the published literatures, to improve implementation effectiveness.

3.2.3 Specific Aim 3: **To assess the awareness, perceptions, and preferences toward genetic testing among the United States general public, and how this may vary by racial-ethnic groups and rural-urban status.**

3.2.3.1 Research Questions:

This aim sought to explore the two following **core research questions**:

1. What are the awareness, perceptions, and preferences regarding genetic testing among minority racial and ethnic populations in the US (including Black, Hispanic, and Asian populations) and how do these differ from Whites?
2. What are the awareness, perceptions, and preferences regarding genetic testing among rural residents and how do these differ from urban populations?

We focused on three key domains of these two research questions: a) awareness, b) preferences, and c) perceptions.

a. **Domain 1: Awareness**.

Question 1: What are the awareness of different types of genetic testing among different racial/ethnic minorities and different geographic populations?

Hypothesis 1: Black, Hispanic, and Asian participants will have differing levels of awareness regarding genetic testing compared with Whites.

Hypothesis 2: Rural residents will have differing levels of awareness regarding genetic testing compared with people residing in urban areas.

b. **Domain 2: Preferences**.

Question 2: What preferences do racial/ethnic minorities and rural-urban populations have towards genetic testing and results?

Hypothesis 3: Black, Hispanic, and Asian participants will have differing preferences for genetic testing and results compared with Whites.

Hypothesis 4: People who reside in the rural area will have differing preferences for genetic testing and results compared with urban residents.

c. **Domain 3: Perceptions.**

Question 3: What are the attitudes, perceived behavioral control, subjective norms, and intentions related to genetic testing among different racial/ethnic minorities and different geographic populations?

Hypothesis 5: Black, Hispanic, and Asian participants will have differing attitudes, perceived behavioral control, subjective norms, and intentions related to genetic testing compared with Whites.

Hypothesis 6: Rural residents will have differing attitudes, perceived behavioral control, subjective norms, and intentions related to genetic testing compared with urban populations.

3.2.3.2 Research Design and Theoretical Framework

A cross-sectional online survey using the Qualtrics panel service was developed to assess the awareness, perceptions, and preferences of racial/ethnic minority populations living in the US on different genetic testing strategies. The Theory of Planned Behavior (TPB), one of the most widely accepted behavior change theories, was used to develop the perception survey items and scales measuring the attitude, perceived behavioral control, subjective norm, and intention constructs.

3.2.3.3 Instrument Development and Measurements

The survey consisted of 3 main topic domains: awareness; preferences; and perceptions. The survey was divided into five sections including 1) demographics, 2) health literacy and numeracy, 3) awareness, and knowledge regarding general genetic testing concepts and strategies, 4) comfort with regards to sampling methods, results sharing, and pharmacogenetic testing (preference domain), and 5) theory of planned behavior questions (perception domain).

Demographic information such as age, gender, race/ethnicity, annual household income, educational level, geographic region, and smoking status were collected. Health literacy and numeracy were assessed using a question adopted from a previous study.[171] In the awareness domain, two genetic testing related questions from the HINTS 5 cycle 4 were adopted. HINTS 5 cycle 4 questions included general knowledge regarding genes and genetic testing, impact of gene inheritance on obesity, cancer, cardiovascular diseases, diabetes, and psychiatric conditions. A total of six genetic testing related statements were added as true or false questions where three

of them asked about risk of diseases and the other three were related to medications. Finally, one specific question about awareness of preemptive vs. reactive pharmacogenetic testing was asked.

In the preferences domain, questions related to comfort around different sampling methods, preferences toward sampling choices, sharing test results with multiple stakeholders, and preemptive vs. reactive pharmacogenetic testing were assessed using both multiple choice items and Likert-type items ranging from very comfortable to very uncomfortable. Finally, we asked the participants about their opinion on impact of COVID-19 pandemic in getting a genetic test.

In the perceptions domain, a set of 15 Likert-type items based on the TPB was asked to investigate participants' attitudes, perceived behavioral control, subjective norms, and intentions related to genetic testing. A series of identical questions was prepared to examine perceptions towards genetic testing for different disease conditions. These sets of questions were divided into two sections including risk of disease and choice of treatments. The risk of disease section is considering Theory of Planned Behavior (TPB) in the context of intention to get a genetic test to predict risk of getting a certain disease. Diseases in the 'risk of disease' section include Alzheimer's disease, cancer, Huntington's disease, and macular degeneration. The choice of treatments section is considering Theory of Planned Behavior (TPB) in the context of intention to get a genetic test to help guide choice of treatment for a certain disease. Diseases in the 'choice of treatments' section included cancer, chronic pain, depression, and heart disease. A complete set of survey questions is presented in the appendix section.

Table 5: Survey Domains and Questions

Domain	Questions	Number & Type of Items
Demographics	1) Sex	1 multiple choice item
	2) Age	1 fill in the blank
	3) Race/Ethnicity	1 multiple choice item
	4) Annual household income	1 multiple choice item
	5) Educational level	1 multiple choice item
	6) Rurality	1 multiple choice item
	7) Geographic information (State, Zip code)	1 drop-down, 1 fill in the blank
	8) Smoking status	1 multiple choice item
	9) Health insurance coverage	1 multiple choice item
	10) Health conditions	1 multiple choice item
Health Literacy and Numeracy	11) Filling out medical forms	1 multiple choice item
Awareness	12) Two questions directly adopted from HINTS cycle 4	1 multiple choice item and 1 Likert-type item
	13) Knowledge statements	6 True or False statements
	14) Pharmacogenetic testing awareness	1 multiple choice item
Preferences	15) Comfort around different sampling methods	3 Likert-type items
	16) Choice of sampling method	1 multiple choice item
	17) Sharing genetic test results	7 Likert-type items
	18) Preferences toward pharmacogenetic testing	1 Likert-type scale
	19) Genetic testing in COVID-19 pandemic	1 multiple choice item

Perceptions	**Risk of Getting Certain Diseases**	20) TPB questions – Alzheimer's disease	15 Likert-type items
		21) TPB questions – cancer	15 Likert-type items
		22) TPB questions – huntington's disease	15 Likert-type items
		23) TPB questions – macular degeneration	15 Likert-type items
	Treatment for Certain Diseases	24) TPB questions - cancer	15 Likert-type items
		25) TPB questions – chronic pain	15 Likert-type items
		26) TPB questions - depression	15 Likert-type items
		27) TPB questions – heart disease	15 Likert-type items

3.2.3.4 Sample Size Calculation

Our target population for this survey were non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Asians, and Hispanics living in the US. We set the significance level as 0.05 and power as 80%, hence the Z score was calculated as 1.96. As we opted to choose 95% confidence level, 0.5 standard deviation, a margin of error (i.e., confidence interval) of ± 5%, and design effect 1 for simple random sampling, the conventional sample size formula[172] for large population is as follows:

$$Sample\ size = \frac{(Z\ score)^2\ \times Std\ Dev\ \times (1 - Std\ Dev)}{(margin\ of\ error)^2}$$

According to the equation above, a total of 384 respondents were required to be included for each of the race/ethnicity and rural-urban groups. Since our target population is significantly large and the calculated sample size did not exceed 5% of the targeted population, we did not have to use the Cochran's correction formula. Therefore, this study aimed to recruit at least 400 individuals for each of these race/ethnicity subgroups.

3.2.3.5 Recruitment

Using a Qualtrics panel, this study aimed to recruit a total of 1,600 participants, including White (n = 400), Black (n = 400), Hispanic (n = 400), and Asian (n = 400) living in the US. Every respondent from the Qualtrics panel selects the languages they speak, read, and/or write, while they are recruited. This enables Qualtrics to target and invite only those respondents that have pre-selected the language of the survey which was English in this case. Demographic information such as sex, age, annual household income, and educational level was collected from the HINTS 5 cycle 4 survey for the quota purpose. This study attempted to recruit a survey cohort identical to the HINTS population based on those selected demographic characteristics, via Qualtrics' demographic quotas. This helps to improve the generalizability of the overall study findings. Demographic quotas for the overall sample are presented in Table 7.

There were no direct benefits to participants, but participants did receive an incentive directly from Qualtrics if they complete the survey. This study protocol was reviewed and approved by IRB as "exempt" and all participants were presented an IRB-approved information letter before proceeding with the survey. There were no monetary costs to participate in this project. The risks involved in this survey were minimal and participation was completely voluntary. Participants was able to withdraw at any time during the survey.

This study pre-tested and pilot-tested the survey to examine the internal validity of the survey instrument. Construct and face validity, as well as the clinical applicability of the survey instrument, was assessed using a group of HORP graduate students (n = 14), College of Pharmacy faculty, and researchers at the main investigator's home institution. To ensure the survey is easy to read and can be finished within appropriate time, it was then pilot-tested in an online soft-launch using a sample of the target population from the Qualtrics panel (n = 100).

This pilot-testing helped to identify variability in responses. Later, the revised version was sent to Qualtrics for the final round.

Table 6: Overall Percentage Quotas for Qualtrics

Characteristic	Percent	Possible frequency (N = 1600)
Sex		
Male	42%	672
Female	58%	928
Race/ethnicity		
Non-Hispanic Black or African American	25%	400
Non-Hispanic White	25%	400
Non-Hispanic Asian	25%	400
Hispanic or Latino(a)	25%	400
Age		
18-34 years	14%	224
35-49	20%	320
50-64	31%	496
65-74	23%	368
75+	12%	192
Rurality		
Rural	50%	800
Urban	50%	800
Annual household income level		
<$20,000	16%	256
$20,000-$49,999	26%	416
$50,000-$74,999	18%	180
$75,000-$99,999	12%	288
$100,000-$199,999	21%	336
>$200,000	7%	112
Education level		
No high school diploma	6%	96
High school diploma or GED	18%	180
Some college	30%	480
Bachelor's degree	27%	432
Post-Baccalaureate Degree	19%	304

3.2.3.6 Data Collection

US adults aged 18 years old and above were eligible for participation if they identified themselves as either non-Hispanic White, non-Hispanic Black, Hispanic, or non-Hispanic Asian.

3.2.3.7 Statistical analysis

Descriptive statistics were used to analyze the respondents' characteristics. Internal consistency i.e., reliability was assessed using Cronbach's alpha to a standard of ≥ 0.70. Comparisons between different racial-ethnic groups and rural-urban respondents for awareness and preference sections were made using chi-square tests. In some cases, the 5-point Likert-type items were recategorized into three categories to facilitate the analyses. For example, very comfortable and comfortable were merged to comfortable, while very uncomfortable and uncomfortable were coded as uncomfortable. Suburban and urban were collapsed into 'urban' for analyses.

To further analyze the TPB questions, we created composite variables for intention, attitude, subjective norm, and perceived behavioral control by converting the Likert-type items into a scale score and recoded any negatively worded responses. Of note, items 2 and 3 in the PBC construct were reverse coded for analysis. Scale scores for each construct were created by adding the item scores (ranging from 1=Strongly Disagree to 5=Strongly Agree) for each item in the construct, then dividing by the total number of items in that construct (Attitudes=4 items, PBC=5 items, Subjective Norms=3 items, Intention=3 items). Continuous scale scores ranged from 1 to 5, with higher values indicating higher/more positive attitude, PBC, subjective norms, or intention. Mean with standard deviation, as well as median scale scores were calculated for

each TPB construct. Both ANOVA and t-test was used to compare the mean TPB scale scores between different racial-ethnic groups and rural-urban respondents. Significant comparisons were identified using ANOVA with Tukey's post-hoc analysis for racial and ethnic groups.

To investigate predictors of intention to get a genetic test, logistic regression models were run. The dependent variable was the intention scale score ("intention") dichotomized into low intention (less than median scale score) and high intention (median and above). This process of dichotomizing continuous outcomes using median split is supported by the existing literature.[173-176] While we may lose statistical power when we dichotomize a continuous variable to a categorical variable, our data set is large which may help address this concern. Secondly, by running logistic regression models, the results can be easily interpreted and comprehended by lay persons. We set intention as a dependent variable, and the scale scores of attitude, subjective norm, perceived behavioral control, and demographic characteristics as the predictor variables. The logistic regression was then repeated for each of the four diseases in both risk of disease section and choice of treatments section. Associations in all these regression models was reported as odds ratios (OR) along with their 95% confidence intervals (CI) and presented in a figure. Demographic characteristics and health literacy and numeracy was also considered as predictor variables for these regression models. All the statistical analyses were performed in SAS 9.4 and the P value was set to 0.05.

3.2.3.8 Expected outcomes

The expected outcomes of this aim were: 1) minorities will have differing level of awareness regarding genetic testing strategies compared with Whites; 2) rural residents will have differing levels of awareness regarding genetic testing strategies compared with people residing

in urban areas; 3) minorities will have differing preferences for genetic testing strategies compared with Whites; 4) people who reside in rural areas will have differing preferences for genetic testing strategies compared with urban residents; 5) minorities will have different attitudes, perceived behavioral control, subjective norms, and intentions related to genetic testing compared with Whites; 7) rural residents will have different attitudes, perceived behavioral control, subjective norms, and intentions related to genetic testing compared with urban populations; and 8) several demographic characteristics such as age, sex, socioeconomic status, income, education, and geographic location will act as significant predictors in logistic regression models assessing effects of race/ethnicity and rural-urban areas on perceptions, awareness, and preferences regarding genetic testing.

Chapter Four

Results

Results are presented separately for aims 1, 2, and 3. For aim 1, findings from the road network analysis are reported, overall and by state. Findings were stratified by race to identify the key differences in racial characteristic between people living in different travel time categories such as less than 30 minutes, 30 to 59 minutes, 60 to 119 minutes, 120 to 179 minutes, and 180 minutes and above. Regarding aim 2, results from the scoping review were presented with a list of barriers and facilitators to pharmacogenetic testing implementation. These barriers and facilitators were reported using the five major domains of CFIR theoretical framework. Finally, we presented our Qualtrics survey findings which includes 1,600 US general population. The survey aimed to understand awareness, perceptions, and preferences about genetic testing concepts and strategies among the US general public. Findings were then compared among different racial-ethnic and rurality subgroups.

4.1. Aim 1 results

Specific Aim 1. To examine the geographical access to genetic testing centers for people living in the United States.

In this section, we will first report the characteristics of the genetic testing clinics included in this study. These genetic testing clinics are the destinations of our road network analysis. Next, we will summarize the driving time results based on the racial characteristic for

the entire US population. Finally, we will report driving time results by the seven genetic regional networks and findings will be stratified by race.

4.1.1. Genetic Testing Clinic Characteristics

A total of 1,284 genetic testing clinic locations were retrieved from the website of American College of Medical Genetics and Genomics (ACMG). Each of these genetic testing clinics had a short description of their attributes in the webpage. These attributes are summarized in table 1 below. In total, there were seven regional genetics network including Heartland, Midwest, Mountain states, New England, New York Mid Atlantic, Southeast, and Western states. New York Mid Atlantic and Southeast had the highest number of genetic testing clinics, 445 (35%) and 246 (19%) respectively. Other regions had a similar number of genetic testing clinics, ranging from 8% to 10%. In total, 658 (51%) genetic testing clinics mentioned that they provide genetic counseling services. With regards to specialties, cancer related genetic testing was reported in most locations (32%) followed by prenatal (27%) and pediatric (23%) specialties. The majority of the clinics did not provide information on whether they accept Medicaid services, however more than a quarter of those reported accepting Medicaid. Only 47 (4%) genetic testing clinics mentioned providing telehealth services. It is notable that different clinics can be affiliated with the same institution or can have similar specialties. Less than half (46.65%) reported whether they were affiliated with an academic institution. Of those that reported, less than 10% of genetic testing clinics (9%, 56 out of 599) were affiliated with an academic institution.

Further examining the genetic testing clinics data, we later found 55 duplicates in these 1,284 records based on the addresses provided. In addition, selecting the unique institutions

affiliated, we further excluded 502 duplicates. Therefore, 782 unique genetic testing clinics remained. However, it is understood that multiple clinics may have affiliated with the same institution which makes it difficult to identify the unique genetic testing clinics. Even those genetic testing clinics with the same addresses had different clinic name or institution affiliated which ultimately required us to present the characteristics table 1 based on the original data retrieved. Hence, the table 1 results should be interpreted with caution. Most importantly, calculating the distance between an origin and a destination point provides the same driving time regardless of whether destinations are duplicates or not. For example, the distance between a single point A and a single point B is exactly similar to the distance between a single point A and multiple points of B. Fundamentally, it was not necessary to remove the duplicates to answer the research question.

Table 7: Genetic Testing Clinic Characteristics

Characteristics	Genetic Testing Clinics (n, %)
Observations	1,284
Regional Genetics Network	
New York Mid Atlantic	445 (34.66%)
Southeast	246 (19.16%)
Heartland	131 (10.20%)
Western States	121 (9.42%)
New England	119 (9.27%)
Mountain States	114 (8.88%)
Midwest	108 (8.41)
Counseling	
Yes	658 (51.25%)
Not reported	626 (48.75%)
Specialties (one clinic can have multiple specialties)	
Cancer	413 (32.17%)
Prenatal	344 (26.79%)
Pediatric	289 (22.51%)
Reproductive	156 (12.15%)
Cardiovascular	125 (9.74%)
Neurogenerative	26 (2.02%)
Accept Medicaid	
Yes	344 (26.79%)
No	29 (2.26%)
Not reported	911 (70.95%)
Telehealth	
Yes	47 (3.66%)
No	1 (0.001%)
Not reported	1176 (91.59%)
Academic Institution	
Yes	56 (4.36%)
No	543 (42.29%)
Not reported	685 (53.35%)

4.1.2. Overall Findings

Out of the available 85,427 census tracts, 32 census tracts were excluded because no race data was available for the Virgin Islands and 614 census tracts were excluded from the analysis because no population lived in those census tracts. According to the US Census 2020 data, a total of 334,735,155 populations lived in those 84,781 census tracts where more than 204 million were Whites. Around 41 million Black or African American population and 20 million Asians were living across the US. More than 68 million people were included in the other group which is defined as American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and some other races who do not identify with any of the traditional race categories as well as multiracial population. Significantly different racial groups lived in different driving time categories ($P < 0.0001$). More than 210 million people in 52,451 census tracts had greater access because they were living within 30 minutes driving distance to a nearest genetics clinic. Only 58% of Whites living in the US had access to a nearest clinic within 30 minutes driving distance. At the same driving distance, a higher percentage of Blacks (73%) and Asians (82%) had access to a nearest clinic. Further, around 3.2 million people, 1% of the entire US population, living in 967 census tracts had to drive 180 minutes and higher to go to a nearest genetic clinic. Compared to the Black and Asians, 30-to-40-fold Whites were living outside of this 180-minute driving distance. These overall findings are summarized in table 2. The table is using column percentages for easy interpretation where the column percentages will add up to 100%. For example, from table 2, 63% of the total population were living withing 30 minutes driving zone of a genetic testing clinic.

Table 8: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories

Driving Time Categories	Total Census Tracts	Total Population	Total White Population	Total Black Population	Total Asian Population	Total Others*
Less than 30 minutes	52,451	210,928,381 (63.01%)	118,982,668 (58.09%)	30,341,326 (73.41%)	16,225,417 (81.58%)	45,378,970 (66.08%)
30 to 59 minutes	17,270	71,447,867 (21.34%)	49,219,662 (24.03%)	6,540,363 (15.82%)	2,813,541 (14.15%)	12,874,301 (18.75%)
60 to 119 minutes	11,376	40,176,732 (12.00%)	28,403,903 (13.87%)	3,779,912 (9.15%)	679,197 (3.41%)	7,313,720 (10.65%)
120 to 179 minutes	2,717	8,986,107 (2.68%)	6,190,497 (3.02%)	603,276 (1.46%)	121,824 (0.61%)	2,070,510 (3.01%)
180 minutes and over	967	3,196,068 (0.95%)	2,041,135 (1.00%)	68,034 (0.16%)	50,071 (0.25%)	1,036,828 (1.51%)
Total	**84,781**	**334,735,155**	**204,837,865**	**41,332,911**	**19,890,050**	**68,674,329**

*Others included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and some other races who do not identify with any of the traditional race categories as well as multiracial population

4.1.3. Findings for Specific Regions

Different driving distance categories had significantly different racial groups in each of the 7 regional networks, 50 individual states, District of Columbia, and Puerto Rico ($P < 0.001$). The appendix table S1 contains the findings regarding these seven regional networks stratified by race. Mountain State had the highest number of census tracts (n = 385) located outside of 180 minutes driving distance. Out of the 3.2 million people who were living outside of 180 minutes driving zone in the entire US, a total of 1.4 million people were resided in the Mountain States region alone. Western state had the second highest number of census tracts (n = 281) located outside 180 minutes driving zone, and around one million people lived there. Midwest region had around half a million people living outside of 180 minutes driving zone in 186 census tracts. In contrast, New England region had only 6 census tracts with a population of 14,255 living outside the 180 minutes region.

Findings for each state are summarized in narrative, tables, and graphs based on the seven regional genetics network below. The graphs presented in this aim will be similar to the example graph below (Figure 5). For each region, we will present one graph with multiple states. According to this example graph, 88% of the Black living in South Dakota were living within 30 minutes driving distance.

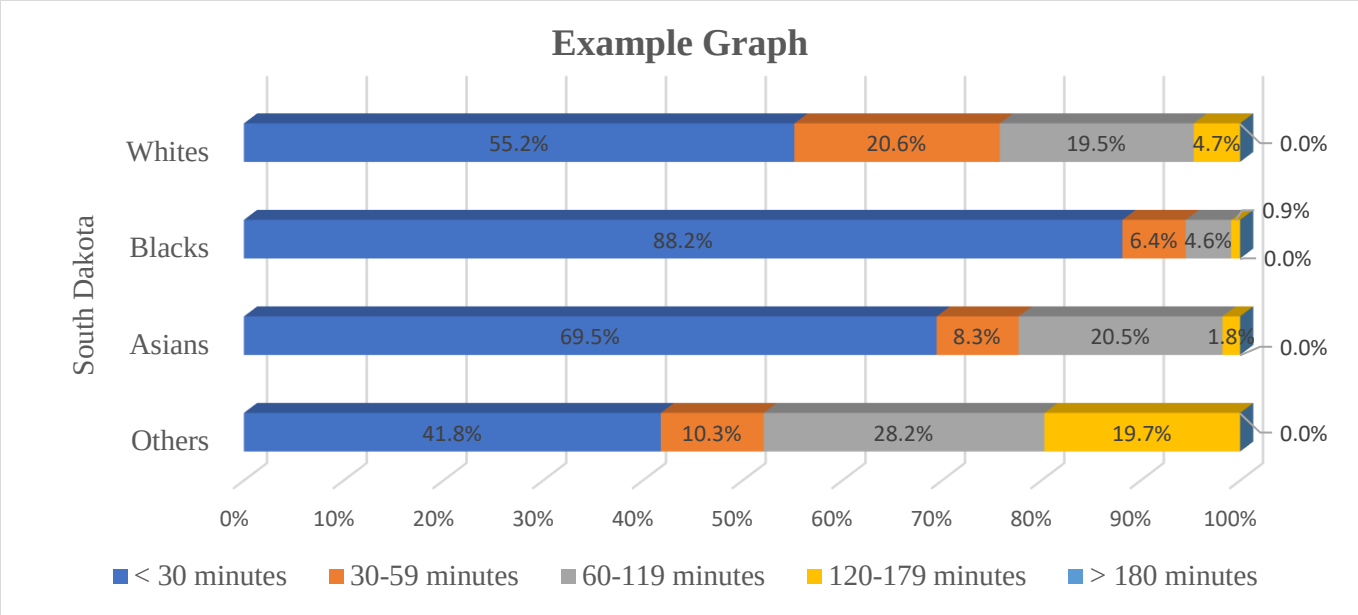


Figure 5: Example Graph

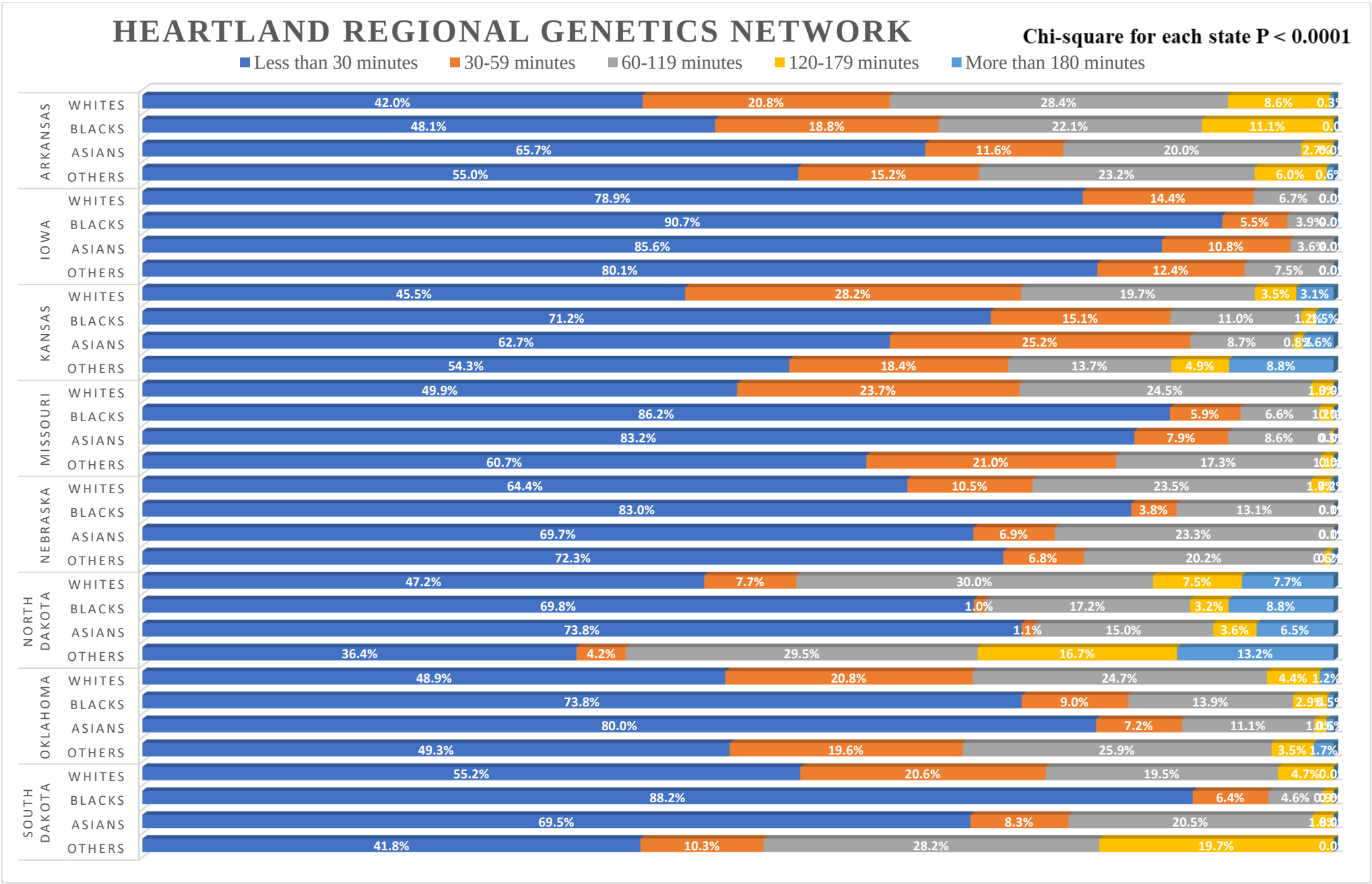
4.1.3.1. Heartland Regional Genetics Network

A total of 8 states were included in this network (Table 3). Less than 50% of the total population of Arkansas, Kansas, and North Dakota had access to a nearest genetic testing clinic within 30 minutes driving distance. Among the 8 states, Kansas had the highest number of populations, around 110 thousand people (4%) in total of 38 census tracts, were living outside of the 180-minutes driving zone. North Dakota had the highest percentage of people, around 8% of their total population, who had to drive 180 minutes or more to go to a nearest genetic testing clinic. Iowa, Missouri, and South Dakota had no census tract outside of 180 minutes driving distance while only one census tract in Nebraska was included in that category.

When looking at the racial breakdown per state and per driving time to the nearest testing clinic, around two-third of the Asians in Arkansas lived within the 30 minutes driving distance compared to 42% Whites and 48% Black (Figure 1). In Kansas, 71% of the Black were living inside the 30-minutes driving zone compared to 46% White and 63% Asians. Only 47% Whites lived within 30-minutes driving distance in North Dakota compared to 70% Black and 74% Asians. In North Dakota, higher percentage of Black were living outside of 180-minutes driving distance compared to Whites (9% vs. 8%). Compared to Black, 5-fold more Whites had to drive around at least 2 hours to go to a nearest genetic clinic in South Dakota.

Table 9: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Heartland Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Arkansas	Less than 30 minutes	328	1,354,921 (44.99%)
	30-59 minutes	165	589,618 (19.58%)
	60-119 minutes	245	801,529 (26.62%)
	120-179 minutes	82	256,164 (8.51%)
	More than 180 minutes	3	9,292 (0.31%)
Iowa	Less than 30 minutes	713	2,541,500 (79.66%)
	30-59 minutes	116	438,332 (13.14%)
	60-119 minutes	65	210,537 (6.60%)
	120-179 minutes	0	0
	More than 180 minutes	0	0
Kansas	Less than 30 minutes	397	1,436,232 (48.89%)
	30-59 minutes	189	758,106 (25.80%)
	60-119 minutes	167	526,460 (17.92%)
	120-179 minutes	34	102,413 (3.49%)
	More than 180 minutes	38	114,669 (3.90%)
Missouri	Less than 30 minutes	915	3,516,094 (57.13%)
	30-59 minutes	322	1,287,114 (20.91%)
	60-119 minutes	387	1,252,914 (20.36%)
	120-179 minutes	30	98,791 (1.61%)
	More than 180 minutes	0	0
Nebraska	Less than 30 minutes	375	1,305,213 (66.54%)
	30-59 minutes	46	187,698 (9.57%)
	60-119 minutes	121	442,080 (22.54%)
	120-179 minutes	10	22,400 (1.14%)
	More than 180 minutes	1	4,113 (0.21%)
North Dakota	Less than 30 minutes	83	366,886 (47.09%)
	30-59 minutes	24	54,119 (6.95%)
	60-119 minutes	76	227,646 (29.22%)
	120-179 minutes	29	65,158 (8.36%)
	More than 180 minutes	16	65,285 (8.38%)
Oklahoma	Less than 30 minutes	615	2,041,047 (51.55%)
	30-59 minutes	217	762,376 (19.26%)
	60-119 minutes	298	948,425 (23.95%)
	120-179 minutes	55	157,867 (3.99%)
	More than 180 minutes	19	49,638 (1.25%)
South Dakota	Less than 30 minutes	107	478,500 (53.97%)
	30-59 minutes	52	164,094 (18.51%)
	60-119 minutes	61	182,776 (20.61%)
	120-179 minutes	22	61,297 (6.91%)
	More than 180 minutes	0	0



*Others group included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial

Figure 6: Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Heartland Regional Genetic Network

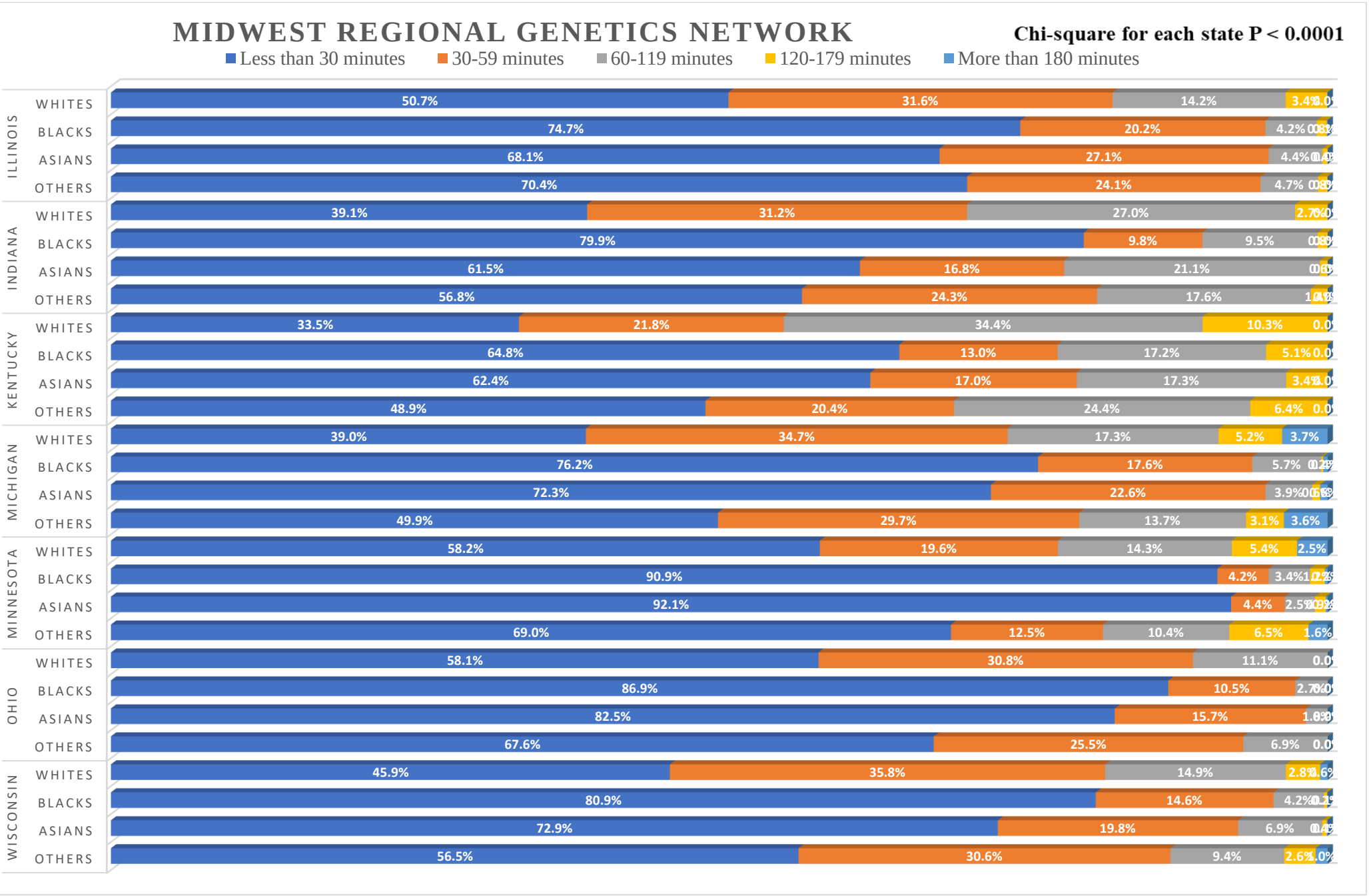
4.1.3.2. Midwest Regional Genetics Network

A total of 7 states were included in this regional genetic network (Table 4). Only 38% of Kentucky population had access to a nearest genetic testing clinic within 30 minutes driving distance. More than half of the population residing in Indiana and Michigan were outside of 30 minutes driving zone. Illinois had only one census tract outside of 180-minutes driving zone. Michigan had the highest number of census tracts, more than 300,000 people in 119 census tracts, living outside the 180-minutes followed by Minnesota, around 120 thousand people in 53 census tracts.

When looking at the racial distribution within each state, around 4% of the Whites living in Michigan were outside of 180-minutes driving distance but less than a percent of Blacks and Asians were in that category (Figure 2). Similarly, 10-to-15-folds higher percentages of Whites had to drive 180 minutes or more to go to a nearest genetic testing clinic when compared to Blacks and Asians in Minnesota. Wisconsin had 29,295, around 1%, White people who were outside of 180-minutes driving zone compared to Blacks and Asians, 190 and 119 people respectively.

Table 10: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Midwest Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Illinois	Less than 30 minutes	1915	7,531,999 (58.79%)
	30-59 minutes	854	3,627,776 (28.31%)
	60-119 minutes	391	1,342,833 (10.48%)
	120-179 minutes	100	304,952 (2.38%)
	More than 180 minutes	1	4,948 (0.04%)
Indiana	Less than 30 minutes	759	3,085,734 (45.48%)
	30-59 minutes	431	1,903,663 (28.05%)
	60-119 minutes	453	1,639,388 (24.16%)
	120-179 minutes	46	156,743 (2.31%)
	More than 180 minutes	0	0
Kentucky	Less than 30 minutes	455	1,699,929 (37.73%)
	30-59 minutes	264	940,494 (20.87%)
	60-119 minutes	443	1,440,110 (31.96%)
	120-179 minutes	142	425,303 (9.44%)
	More than 180 minutes	0	0
Michigan	Less than 30 minutes	1368	4,654,850 (46.19%)
	30-59 minutes	849	3,171,931 (31.48%)
	60-119 minutes	444	1,508,775 (14.97%)
	120-179 minutes	153	423,205 (4.20%)
	More than 180 minutes	119	318,570 (3.16%)
Minnesota	Less than 30 minutes	897	3,618,202 (63.40%)
	30-59 minutes	236	968,828 (16.98%)
	60-119 minutes	219	714,186 (12.52%)
	120-179 minutes	96	283,356 (4.97%)
	More than 180 minutes	53	121,922 (2.14%)
Ohio	Less than 30 minutes	2068	7,447,100 (63.11%)
	30-59 minutes	802	3,236,097 (27.43%)
	60-119 minutes	287	1,115,438 (9.45%)
	120-179 minutes	1	813 (0.01%)
	More than 180 minutes	0	0
Wisconsin	Less than 30 minutes	775	2,949,491 (50.04%)
	30-59 minutes	465	1,969,650 (33.42%)
	60-119 minutes	216	788,264 (13.37%)
	120-179 minutes	57	150,814 (2.56%)
	More than 180 minutes	13	35,499 (0.60%)



*Others group included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial

Figure 7: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Midwest Regional Genetics Network

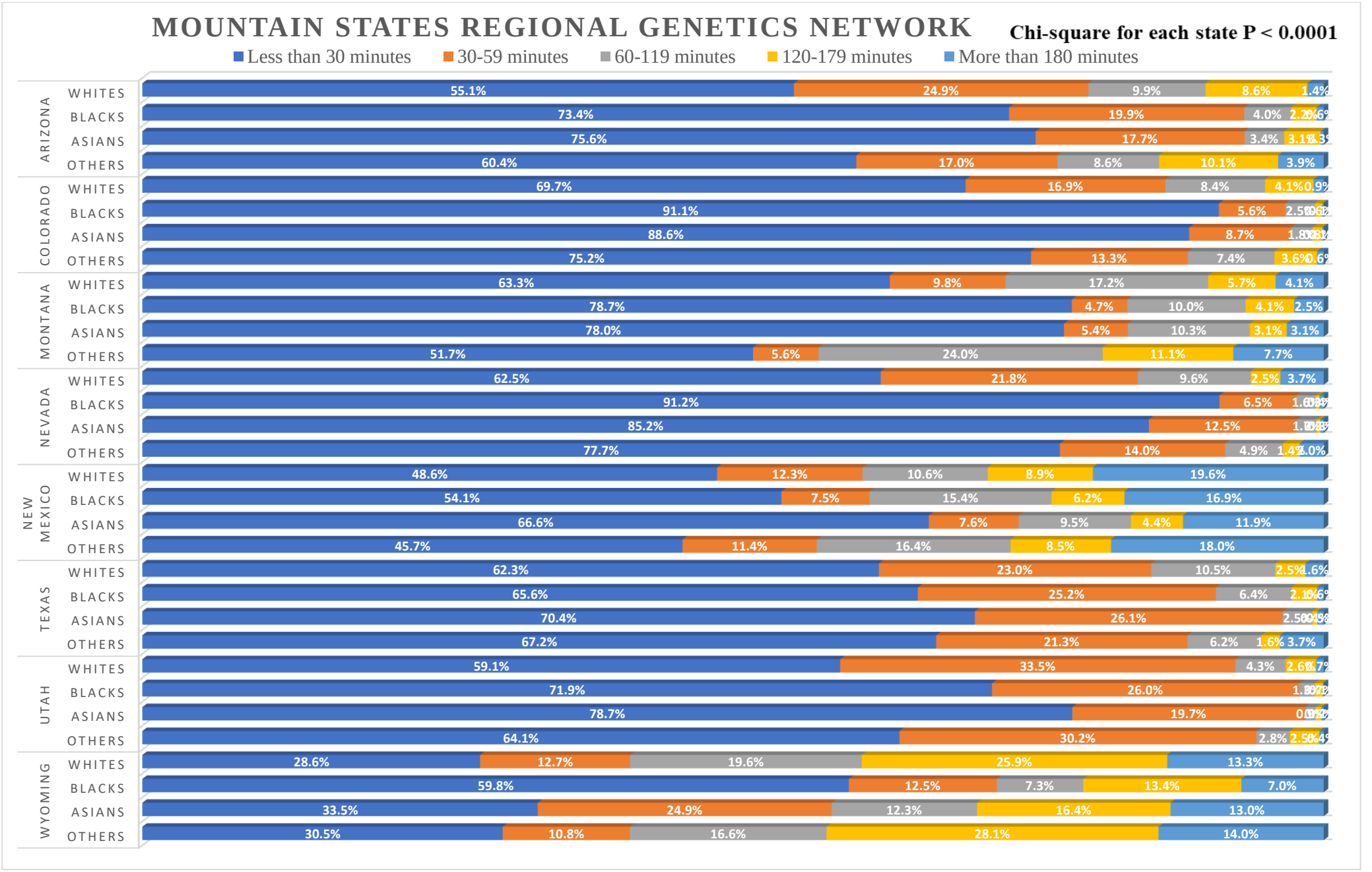
4.1.3.3. Mountain States Regional Genetics Network

A total of 8 states were included in this regional genetic network (Table 5). Colorado had almost 90% of its population living within 30 minutes driving distance. However, compared to around 90% Blacks and Asians, less than 70% Whites lived inside 30 minutes driving zone (Figure 3). All these mountain states had several census tracts outside of 180-minutes driving zone. Specifically, New Mexico and Texas had 247 census tracts altogether that included around a million people living outside of 180-minutes driving distance. Twenty percent of Whites and 17% of Blacks, compared to 12% of Asians, were living outside of 180-minutes driving distance in New Mexico. Texas had 604,140 people, 2% of its total population, driving 180 minutes or higher to go to a nearest genetic testing clinic. Thirteen percent of Whites and Asians, compared to 7% of Blacks, living in the 40 census tracts of Wyoming state had to drive at least 180 minutes to go to a nearest genetic testing clinic.

Table 11: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Mountain States Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Arizona	Less than 30 minutes	993	4,175,573 (58.39%)
	30-59 minutes	342	1,570,133 (21.96%)
	60-119 minutes	182	643,731 (9.00%)
	120-179 minutes	192	613,598 (8.58%)
	More than 180 minutes	44	148,467 (2.08%)
Colorado	Less than 30 minutes	978	4,180,033 (88.60%)
	30-59 minutes	226	888,315 (15.39%)
	60-119 minutes	141	446,461 (7.73%)
	120-179 minutes	74	215,982 (3.74%)
	More than 180 minutes	20	42,923 (0.74%)
Montana	Less than 30 minutes	167	670,115 (61.81%)
	30-59 minutes	31	98,893 (9.12%)
	60-119 minutes	71	195,843 (18.06%)
	120-179 minutes	30	69,912 (6.45%)
	More than 180 minutes	20	49,462 (4.56%)
Nevada	Less than 30 minutes	527	2,231,600 (71.88%)
	30-59 minutes	139	531,108 (17.11%)
	60-119 minutes	64	207,622 (6.69%)
	120-179 minutes	16	54,843 (1.77%)
	More than 180 minutes	26	79,441 (2.56%)
New Mexico	Less than 30 minutes	271	1,011,158 (47.75%)
	30-59 minutes	75	247,472 (11.69%)
	60-119 minutes	89	281,681 (13.30%)
	120-179 minutes	57	181,829 (8.59%)
	More than 180 minutes	117	395,382 (18.67%)
Texas	Less than 30 minutes	4501	18,866,954 (64.73%)
	30-59 minutes	1401	6,676,940 (22.91%)
	60-119 minutes	666	2,392,790 (8.21%)
	120-179 minutes	170	604,681 (2.07%)
	More than 180 minutes	130	604,140 (2.07%)
Utah	Less than 30 minutes	410	1,981,886 (60.58%)
	30-59 minutes	247	1,062,317 (32.47%)
	60-119 minutes	29	127,271 (3.89%)
	120-179 minutes	22	81,216 (2.48%)
	More than 180 minutes	5	18,926 (0.58%)
Wyoming	Less than 30 minutes	46	168,244 (29.17%)
	30-59 minutes	19	72,323 (12.54%)
	60-119 minutes	32	109,798 (19.03%)
	120-179 minutes	40	149,784 (25.97%)

	More than 180 minutes	23	76,702 (13.30%)



*Others group included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial

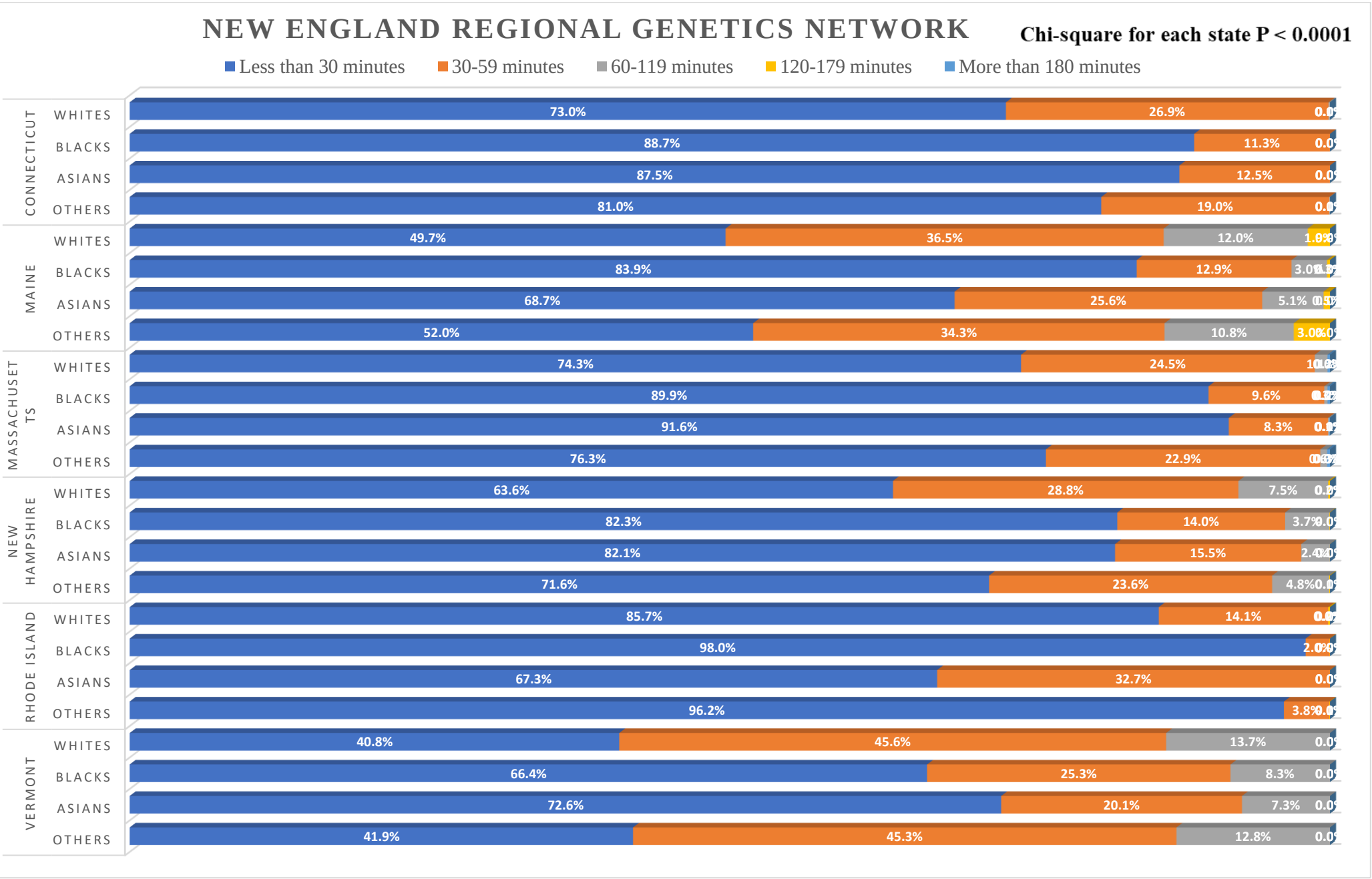
Figure 8: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Mountain States Regional Genetics Network

4.1.3.4. New England Regional Genetics Network

A total of six states were included in this regional genetic network (Table 6). People in this region can access the genetic testing center in a relatively short distance; only Massachusetts, had 6 census tract outside of the 180-minutes driving zone. In Massachusetts, a total of 14,255 people were living outside of the 180-minutes driving zone where over 70% of them were Whites (Figure 4). Except for Vermont, all other states had more than half of the population living within the 30-minutes driving zone. Vermont had only 42% of its population living in that driving category. Over three quarter of the residents of Connecticut, Massachusetts, and Rhode Island were living within 30 minutes driving distance.

Table 12: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for New England Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Connecticut	Less than 30 minutes	672	2770316 (76.83%)
	30-59 minutes	203	832417 (23.08%)
	60-119 minutes	1	3211 (0.09%)
	120-179 minutes	0	0
	More than 180 minutes	0	0
Maine	Less than 30 minutes	181	690389 (50.68%)
	30-59 minutes	145	487381 (35.77%)
	60-119 minutes	60	158996 (11.67%)
	120-179 minutes	14	25593 (1.88%)
	More than 180 minutes	0	0
Massachusetts	Less than 30 minutes	1224	5409745 (76.95%)
	30-59 minutes	357	1545873 (21.99%)
	60-119 minutes	19	60044 (0.85%)
	120-179 minutes	0	0
	More than 180 minutes	6	14255 (0.20%)
New Hampshire	Less than 30 minutes	210	894959 (64.97%)
	30-59 minutes	101	383118 (27.81%)
	60-119 minutes	36	97545 (7.08%)
	120-179 minutes	1	1907 (0.14%)
	More than 180 minutes	0	0
Rhode Island	Less than 30 minutes	218	974540 (87.50%)
	30-59 minutes	27	121429 (12.37%)
	60-119 minutes	0	0
	120-179 minutes	1	1410 (0.13%)
	More than 180 minutes	0	0
Vermont	Less than 30 minutes	72	268795 (41.80%)
	30-59 minutes	91	288082 (44.80%)
	60-119 minutes	29	86200 (13.40%)
	120-179 minutes	0	0
	More than 180 minutes	0	0



*Others group included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial

Figure 9: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for New England Regional Genetics Network

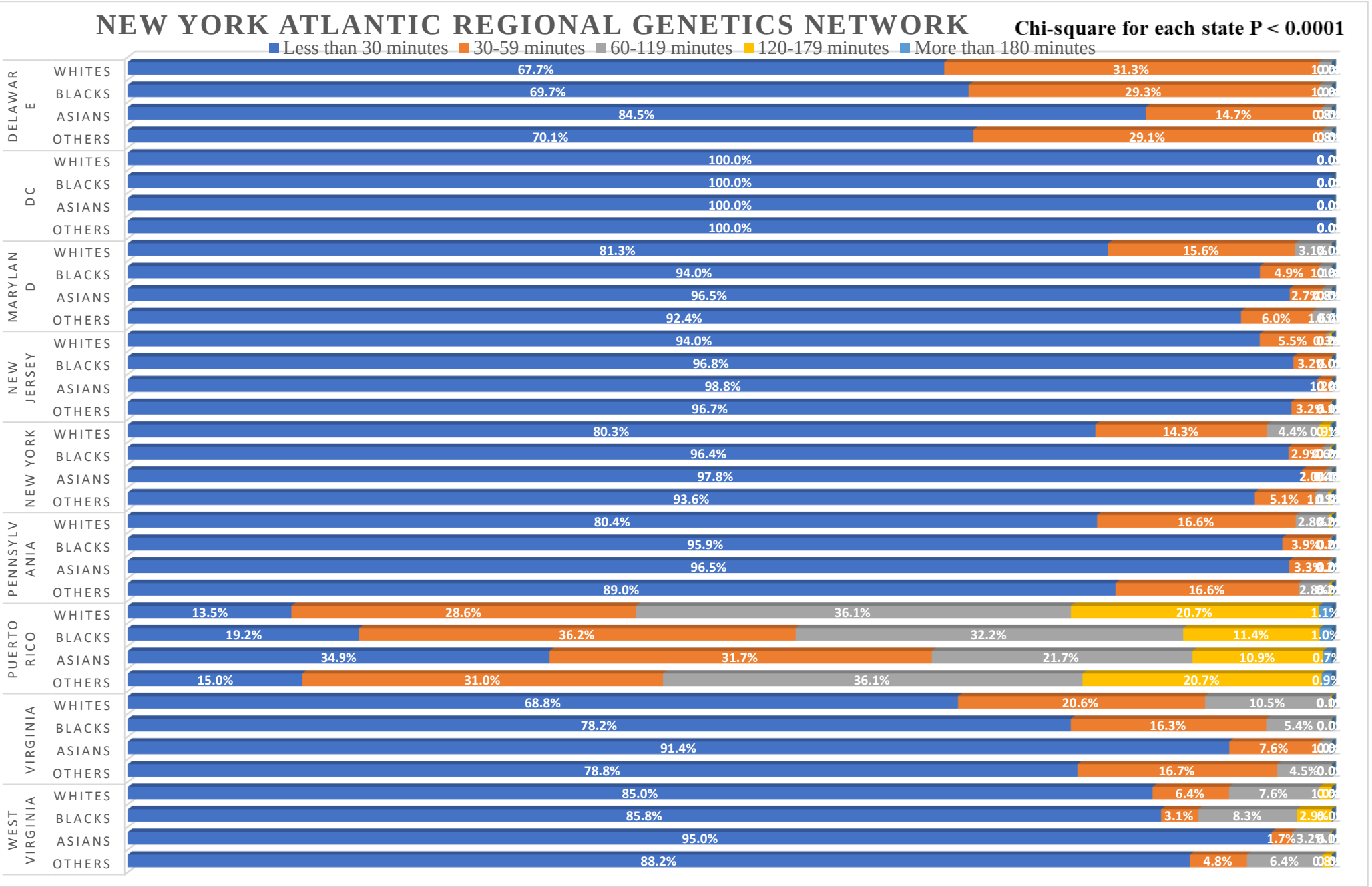
4.1.3.5. New York Mid Atlantic Regional Genetics Network

A total of 9 states were considered as New York Mid Atlantic Regional Genetics Network including the District of Columbia (Table 7). All the census tracts containing around 700 thousand population in the District of Columbia were inside the 30 minutes driving distance zone. Majority of the people of Maryland, New Jersey, New York, and West Virginia were living within the 30 minutes driving distance while Puerto Rico had only 15% of its population in that category. Above 90% of Whites, Blacks, and Asians had greater access to a nearest genetic testing clinic in New Jersey (Figure 5). Most Puerto Ricans (35%) had to drive at least an hour to go to a nearest genetic testing clinic. The majority of the Asians living in Puerto Rico had greater access to a nearest genetic testing clinic i.e., within 30-minutes driving distance when compared to Whites and Blacks. Only New York and Puerto Rico had census tracts, in total 6 and 12 respectively, outside of 180-minutes driving zone.

Table 13: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for New York Mid Atlantic Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Delaware	Less than 30 minutes	184	684875 (69.18%)
	30-59 minutes	72	295289 (29.83%)
	60-119 minutes	2	9784 (0.99%)
	120-179 minutes	0	0
	More than 180 minutes	0	0
District of Columbia	Less than 30 minutes	206	689545 (100%)
Maryland	Less than 30 minutes	1289	5421456 (87.77%)
	30-59 minutes	144	625951 (10.13%)
	60-119 minutes	27	129817 (2.10%)
	120-179 minutes	0	0
	More than 180 minutes	0	0
New Jersey	Less than 30 minutes	2052	8865156 (95.44%)
	30-59 minutes	115	397257 (4.28%)
	60-119 minutes	5	15555 (0.17%)
	120-179 minutes	3	11026 (0.12%)
	More than 180 minutes	0	0
New York	Less than 30 minutes	4548	17585362 (87.05%)
	30-59 minutes	585	1927313 (9.54%)
	60-119 minutes	188	555351 (2.75%)
	120-179 minutes	31	116413 (0.58%)
	More than 180 minutes	6	16810 (0.08%)
Pennsylvania	Less than 30 minutes	2818	10870962 (83.61%)
	30-59 minutes	519	1822616 (14.02%)
	60-119 minutes	86	287193 (2.21%)
	120-179 minutes	8	21929 (0.17%)
	More than 180 minutes	0	0
Virginia	Less than 30 minutes	1568	6351239 (73.58%)
	30-59 minutes	403	1580577 (18.31%)
	60-119 minutes	202	692618 (8.02%)
	120-179 minutes	2	6959 (0.08%)
	More than 180 minutes	0	0
West Virginia	Less than 30 minutes	464	1530525 (85.33%)
	30-59 minutes	32	109644 (6.11%)
	60-119 minutes	43	134292 (7.49%)
	120-179 minutes	7	19255 (1.07%)
	More than 180 minutes	0	0
Puerto Rico	Less than 30 minutes	196	494039 (15.04%)
	30-59 minutes	267	1018161 (30.99%)
	60-119 minutes	299	1154735 (35.14%)

	120-179 minutes	159	588957 (17.92%)
	More than 180 minutes	12	29982 (0.91%)



*Others = American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial; DC = District of Columbia

Figure 10: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for New York Mid Atlantic Regional Genetics Network

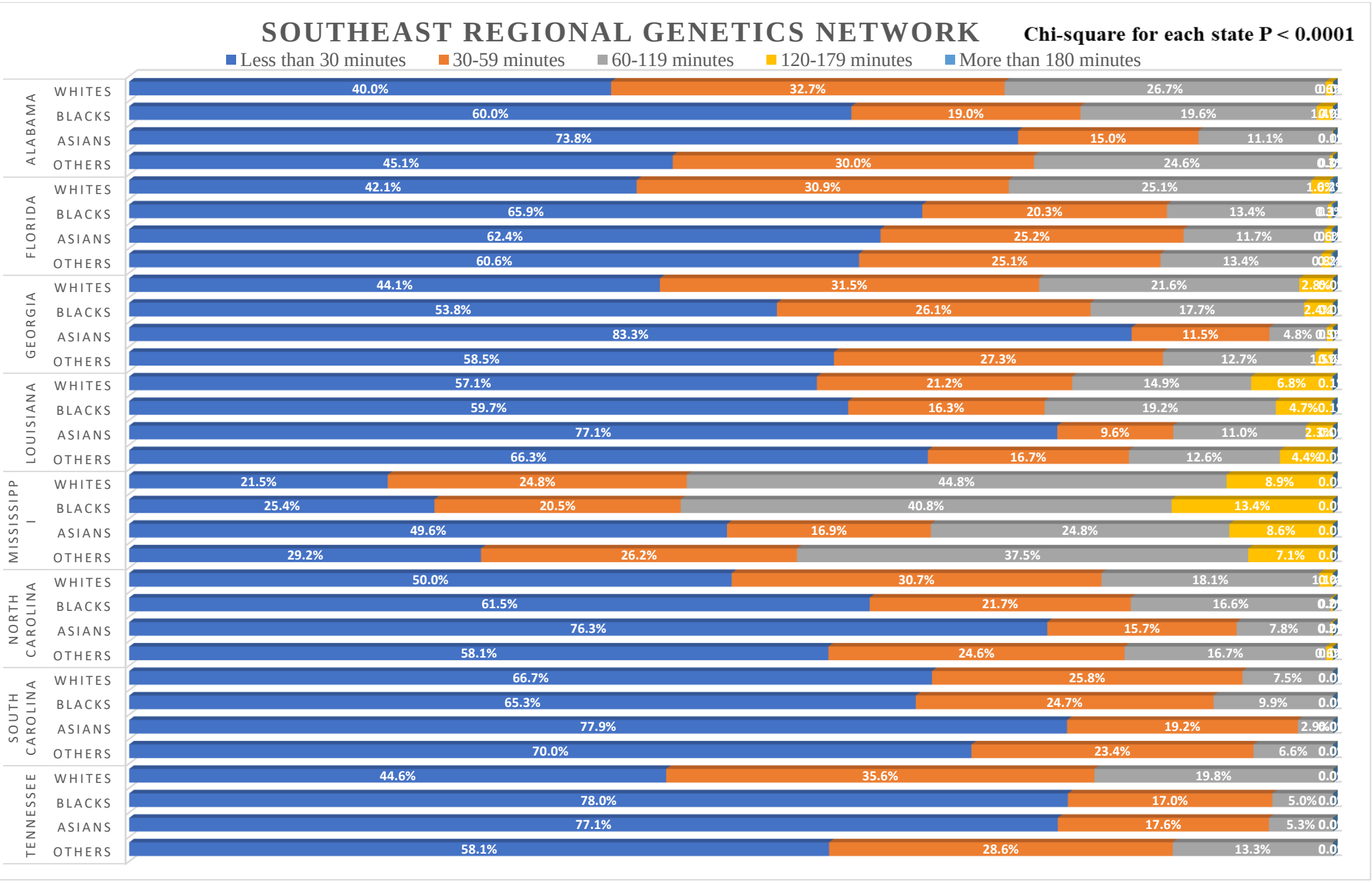
4.1.3.6. Southeast Regional Genetics Network

Out of the included 8 states, only Florida and Louisiana had 12 and 2 census tracts outside of the 180-minutes driving zone, respectively (Table 8). Less than a quarter of Mississippi population living in 201 census tracts were within 30 minutes driving distance to a genetic testing clinic. In Mississippi, only 21% and 25% of Whites and Blacks, respectively, were living in those census tracts compared to half of the Asian population (Figure 6). Further, a higher percentage of Blacks were within 120 to 179-minutes driving zone compared to around 9% of Whites and Asians each living in Mississippi.

Table 14: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Southeast Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Alabama	Less than 30 minutes	633	2317444 (46.12%)
	30-59 minutes	403	1439835 (28.66%)
	60-119 minutes	385	1227883 (24.44%)
	120-179 minutes	13	39117 (0.78%)
	More than 180 minutes	0	0
Florida	Less than 30 minutes	2607	10942016 (50.80%)
	30-59 minutes	1273	5971396 (27.72%)
	60-119 minutes	1116	4330468 (20.11%)
	120-179 minutes	85	251503 (1.17%)
	More than 180 minutes	12	42804 (0.20%)
Georgia	Less than 30 minutes	1373	5427615 (50.67%)
	30-59 minutes	747	3041222 (28.39%)
	60-119 minutes	584	1984274 (18.52%)
	120-179 minutes	80	258797 (2.42%)
	More than 180 minutes	0	0
Louisiana	Less than 30 minutes	792	2756940 (59.19%)
	30-59 minutes	261	885898 (19.02%)
	60-119 minutes	239	742382 (15.94%)
	120-179 minutes	76	269351 (5.78%)
	More than 180 minutes	2	3186 (0.07%)
Mississippi	Less than 30 minutes	201	701399 (23.69%)
	30-59 minutes	197	687983 (23.23%)
	60-119 minutes	382	1263676 (42.67%)
	120-179 minutes	94	308221 (10.41%)
	More than 180 minutes	0	0
North Carolina	Less than 30 minutes	1400	5676457 (54.38%)
	30-59 minutes	726	2872647 (27.52%)
	60-119 minutes	501	1802750 (17.27%)
	120-179 minutes	28	87534 (0.84%)
	More than 180 minutes	0	0
South Carolina	Less than 30 minutes	851	3422124 (66.86%)
	30-59 minutes	332	1289002 (25.18%)
	60-119 minutes	131	407299 (7.96%)
	120-179 minutes	0	0
	More than 180 minutes	0	0
Tennessee	Less than 30 minutes	860	3584158 (51.86%)
	30-59 minutes	516	2182442 (31.58%)
	60-119 minutes	316	1142572 (16.53%)

	120-179 minutes	1	1668 (0.02%)
	More than 180 minutes	0	0



*Others group included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial

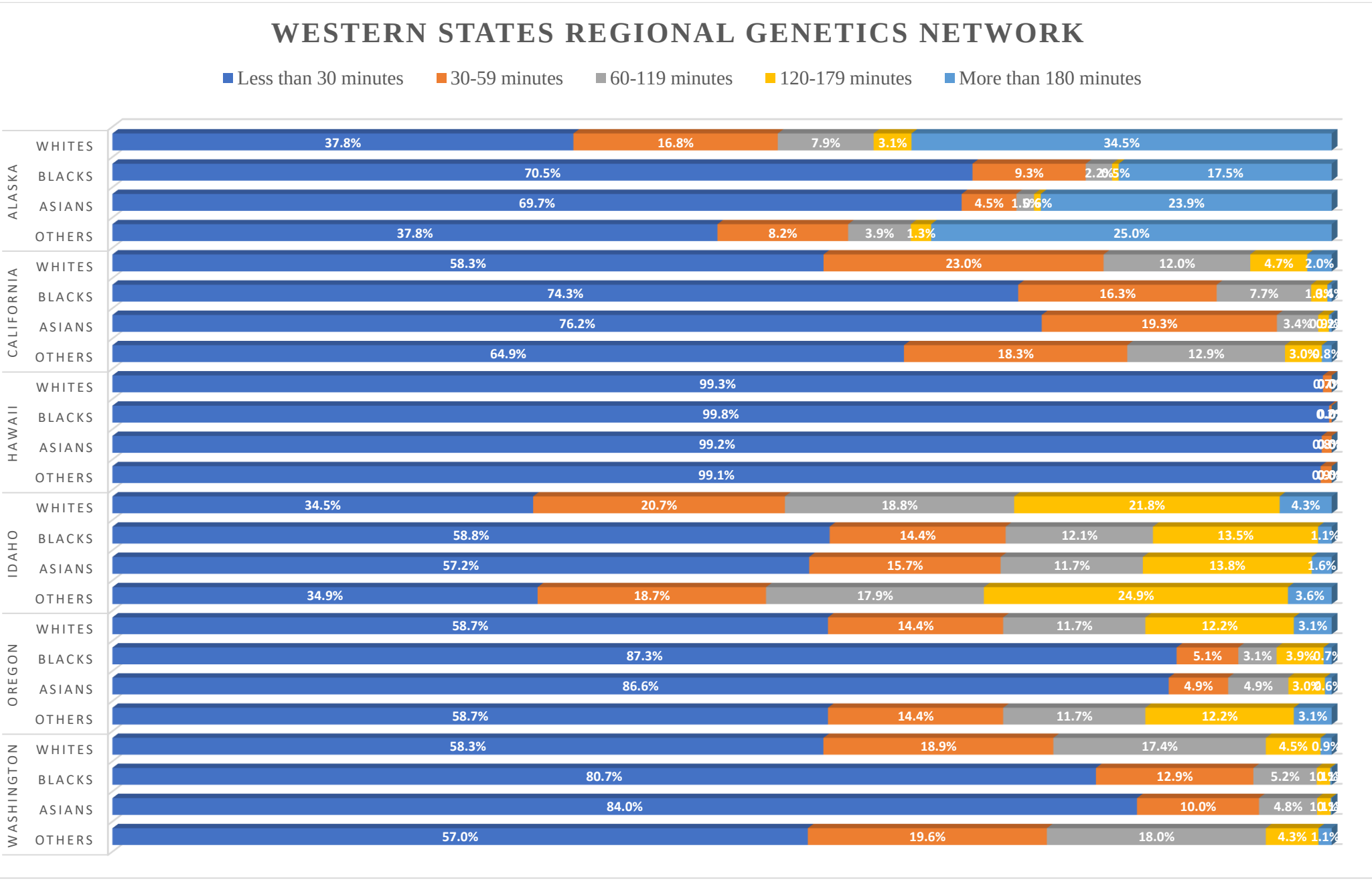
Figure 11: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Southeast Regional Genetics Network

4.1.3.7. Western States Regional Genetics Network

A total of six states were included in this regional genetic network (Table 9). Except for Hawaii, all the states had a substantial number of census tracts outside of 180-minutes driving zone. Alaska had 30% of its total population, more than 220 thousand people, driving 180 minutes or higher to go to a nearest genetic testing clinic. California had 469,506 people living in 136 census tracts, 1% of its total population, outside of 180-minutes driving zone. Majority of the population living outside of 180-minutes driving zone were Whites, estimating around 2% of the total Whites population living in California (Figure 7). Almost all people in Hawaii had greater access to a genetic testing clinic. Idaho had 27 census tracts outside of 180-minutes driving zone that includes 4% of Whites compared to 1-2% of Blacks and Asians. More than 100,000 people residing in 35 census tracts in Oregon had to drive at least 180 minutes or more to go to a genetic testing clinic and the majority of them were Whites. Similarly, Washington had 23 census tracts containing around 65,000 people living outside of 180 minutes driving distance.

Table 15: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Western States Regional Genetics Network

State	Driving Time Groups	Number of Census Tracts	Total Population
Alaska	Less than 30 minutes	83	353732 (48.23%)
	30-59 minutes	19	95947 (13.08%)
	60-119 minutes	10	44429 (6.06%)
	120-179 minutes	5	16844 (2.30%)
	More than 180 minutes	60	222439 (30.33%)
California	Less than 30 minutes	5864	25494311 (64.48%)
	30-59 minutes	1713	8012623 (20.27%)
	60-119 minutes	1042	4267109 (10.79%)
	120-179 minutes	342	1294674 (3.27%)
	More than 180 minutes	136	469506 (1.09%)
Hawaii	Less than 30 minutes	428	1443322 (99.18%)
	30-59 minutes	4	11949 (0.82%)
	60-119 minutes	0	0
	120-179 minutes	0	0
	More than 180 minutes	0	0
Idaho	Less than 30 minutes	166	645568 (35.10%)
	30-59 minutes	81	371988 (20.23%)
	60-119 minutes	93	340308 (18.50%)
	120-179 minutes	89	405802 (22.07%)
	More than 180 minutes	27	75440 (4.10%)
Oregon	Less than 30 minutes	582	2617776 (61.78%)
	30-59 minutes	121	560421 (13.23%)
	60-119 minutes	124	471173 (11.12%)
	120-179 minutes	131	470575 (11.11%)
	More than 180 minutes	35	117311 (2.77%)
Washington	Less than 30 minutes	1046	4730355 (61.39%)
	30-59 minutes	304	1382009 (17.94%)
	60-119 minutes	309	1220510 (15.84%)
	120-179 minutes	89	307451 (3.99%)
	More than 180 minutes	23	64956 (0.84%)



*Others group included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, some other races as well as multiracial

Figure 12: Overall Frequency of US Population by Race and Driving Time to Genetic Testing Clinics Categories for Western States Regional Genetics Network

4.1.4. Communicating with Genetic Testing Clinics

Since genetic testing clinic locations were obtained from a webpage, it is evident that examining access to genetic testing clinics across the US largely depends on the accuracy of the information provided in that list. To further investigate the reliability of the obtained information, a total of 78 calls were made using the phone numbers provided on the website that includes all the genetic testing clinics in both Alabama and Florida. After deleting the duplicate phone numbers, 61 records retained. In some cases, duplicate phone numbers were associated with a slightly changed address or clinic's name. The website suggested that all the 61 institutions should be able to deliver PGx services. Among them, only 29 (48%) confirmed that they do genetic testing and one clinic said they counsel patients and provide recommendations. In contrast, 13 (21%) genetic testing clinics said they do not test for genetics. Calls were not successful for other locations (n = 19, 31%) because of several reasons including number not in service (n = 8), not answered (n =5), long waiting time (n = 3), wrong number (n = 1), office closed (n = 1), and no number (n = 1). The webpage claimed that the list contains addresses of those genetic clinics that have requested to be listed and American College of Medical Genetics and Genomics (ACMG) does not endorse or warrant the quality of these listed institutions. This analysis suggested that the provided list may not have been updated over time and some institutions that wanted to be listed may not have provided accurate information regarding the testing service.

4.2. Aim 2 Results

Specific Aim 2. A scoping review to synthesize current evidence on the barriers and facilitators to implementation of pharmacogenetic testing in a healthcare setting.

In this section, we will first report the findings from the PRISMA diagram and then we will describe the characteristics of the included studies. Later, we will report the barriers and facilitators of pharmacogenetic testing and will organize it based on the five major domains of CFIR.

4.2.1. Findings from PRISMA

A total of 3,536 articles were retrieved from Ovid Medline (n = 3,750), Web of Science (n = 1,280), and International Pharmaceutical Abstracts (n = 126) after removing the duplicates. Data screening was conducted by S.M.F. i.e., as reviewer 1 and two Pharm.D. students worked jointly as a second independent reviewer. Disagreements were resolved through discussions and consensus among the three reviewers, and further validated by another independent reviewer (C.W.A.). Only 252 articles were retained after title and abstract screening and upon screening the full texts, 58 articles were found matching our inclusion criteria mentioned in Chapter 3. A list of reasons for excluding articles is provided in the PRISMA Flow diagram below along with how potential studies were included or excluded. For all 58 articles, one reviewer (S.M.F.) extracted the data using a semi-structured form that includes the following fields – author and year of publication, setting, PGx type (preemptive vs. reactive), specimen, gene types, laboratory information, and constructs within the five domains of CFIR.

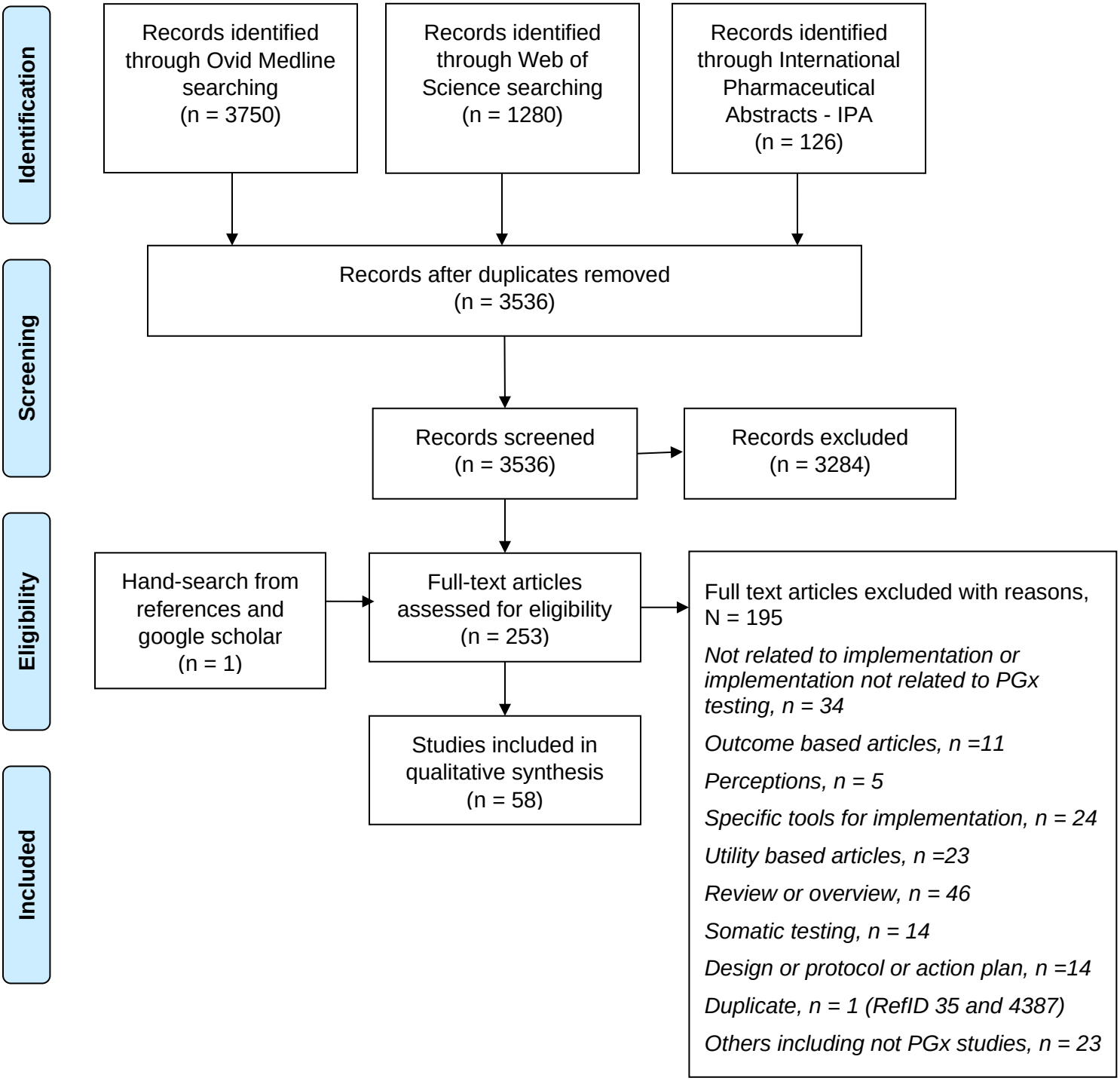


Figure 13: PRISMA Flow Diagram

4.2.2. Overall Characteristics of the Included Studies

Among these 58 publications, 47 unique practice sites were included. In other words, several publications were targeted towards similar implementation projects or genetic testing implementation at the same institution including University of Florida (n = 7), all IGNITE sites (n = 4), Mayo clinic (n = 3), St. Jude's Children Hospital (n = 3), Mission Health (n = 2), North Carolina single pharmacy (n = 2), and Sanford Health (n = 2). Process of implementation along with the barriers and facilitators were presented in multiple publications for the same practice sites, hence it was necessary to include them together in this scoping review. Majority of the included studies (n = 47) were conducted in the United States (US). Four studies were conducted in Canada and Netherlands each while others were from Brazil, New Zealand, and Spain. Although 20 out of the 47 unique practice sites were affiliated with an academic institution, practice sites varied across the included studies. For example, PGx testing was implemented in diverse healthcare settings such as internal medicine clinic, pediatric clinics, emergency departments, integrated community health system, community pharmacies, outpatient clinics, cancer institutes, and psychiatric practice sites etc.

Fourteen of these studies implemented single gene test in their practice settings while others used multigene panel. With regards to sampling, blood (n = 19) and buccal swab (n = 18) were mostly used across the practice settings while saliva was less utilized (n = 4). Although cost of genetic testing was covered by research grants or fundings in most studies, patients had to pay out-of-pocket to cover the test mentioned in three publications.[177-179] Both in-house and outsourced laboratories were used equivalently across different healthcare settings. Specifically, all IGNITE sites, Mission Health, Sanford Health, and practice sites that were affiliated with academic institutions had in-house laboratories to perform the genetic testing. Among all the practice sites that mentioned, turnaround time ranged from 5 days to around 4 weeks regardless of the type of laboratories (in-house vs. outsourced). Clinical Pharmacogenetics Implementation Consortium (CPIC), Pharmacogenomics Knowledgebase (PharmGKB), and Dutch

Pharmacogenetics Working Group (DPWG) were frequently cited as major guidelines followed by these institutions to ensure that genetic testing implementation will have desired outcomes. Table 1 provides a brief overview of the included studies.

Table 16. Overall Characteristics of the Included Studies

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
Marrero et al., 2020[180]		• Preemptive • GatorPGx panel consists of 32 variant alleles across eight pharmacogenes (CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP4F2, CYP2C Cluster, SLCO1B1 and VKORC1) • Blood	• UF Health Pathology laboratory • Unknown
Cicali et al., 2019[22]	• US • University of Florida Health PMP • Funded	• Preemptive • Six drug-gene pairs (CYP2C19-clopidogrel, TPMT-thiopurines, IFNL3-PEGylated interferon alpha based regiments, CYP2D6-opioids, CYP2D6/CYP2C19-SSRI, and CYP2C19-PPIs) • Three of these drug-gene pairs were highlighted in this article • 100% of children offered buccal sample collection consented to enrollment whereas only 73% consented for blood collection. For adults, 89% consented for buccal and blood, separately. • Turn-around time around 10 days	• UF Health Pathology laboratory • Unknown
Weitzel et al., 2018[181]		• TPMT • Blood or buccal swab • Turnaround time of 7 to 14 days	• UF Health Pathology laboratory • Unknown
Weitzel et al., 2014[182]		• CYP2C19 • Genotyping conducted on the Quant Studio™ Open Array utilized a custom genotype array that includes 256 single nucleotide polymorphisms (SNPs) • Blood	• In-house • UF Health Pathology Laboratories (UFHPL) • Laboratories covered the cost of the genotyping for much of the first year but later started billing third party payors
Arwood et al., 2020[183]	• US • University of Florida Health Internal Medicine Clinic • Funded	• CYP2D6 and CYP2C19 • Buccal sample • Median turnaround time 5-6 days	• Mostly UF Health Pathology laboratory, but used external laboratories in a few cases • The pharmacist talked with patient about the cost and if the patient agreed, only then the sample was collected.
Claudio-Campos et al., 2020[184]	• US • University of Florida (UF) Health outpatient Pediatric	• CYP2C19 and CYP2D6 • Blood	• In-house • UF Health Pathology Laboratory • Parents were willing to pay was $235 on average

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
	Psychiatry Clinic • Funded		
Fishe et al., 2020[185]	• US • University of Florida Health Jacksonville Pediatric Emergency Department • Funded	• SNP assay using a targeted AmpliSeq library prep on a NextSeqDx 550 • Buccal swab	• Unknown • Unknown
Empey et al., 2018[186]	• US • All IGNITE research sites • University of Alabama at Birmingham • University of Pennsylvania • University of Florida Health, Jacksonville • University of Illinois at Chicago • University of Florida Health, Shands Hospital, Gainesville • University of Pittsburgh UPMC Presbyterian Hospital • University of North Carolina at Chapel Hill • University of Maryland, Baltimore • Sanford Health • Indiana University • Icahn School of Medicine at Mount Sinai and Hospital • Vanderbilt University • Funded	• CYP2C19-Clopidogrel was the first clinical PGx implementation launched at 9 of the 12 institutions • 8 reactive 4 preemptive • No information on whether they used blood or buccal swab or saliva for PGx testing	• Unknown • All but one of these submitted bills to third party payers or patients for test reimbursement
Levy et al., 2019[98] **Weitzel et al., 2019[116]**	• US • All IGNITE I research sites • Funded	• Both single and multipanel genes • Blood	• Unknown • Developed an interactive pan of test reimbursement

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
Cavallari et al., 2019[102]	• US • 8 Institutions within IGNITE network group • Funded	• CYP2D6 testing • Four institutions genotyped CYP2D6 as part of a multi-gene panel • Four sites had validated assays for blood and either buccal cell or saliva samples • Turnaround time ranged from 2 to 14 business days across sites.	• Six had onsite CAP/CLIA certified laboratory • Cost was described in the discussion section as a barrier but the actual cost of intervention was unknown since it was NIH funded
Rosenmann et al., 2017[187]	• US • Indiana GENomics Implementation: an Opportunity for the Underserved" (INGenious) at Eskenazi Health • Funded	• 14 genes, 43 variants, 28 medications • Unknown type of sample	• Unknown • Supported by National Human Genome Research Institute
Dressler et al., 2018[188]	• US • Mission Health (a rural integrated community health system in the mountains of western North Carolina) • Funded	• CYP2D6 testing for codeine in pediatric patients • Unknown	• In house laboratory (Fullerton Genetics) • Covered by Medicare or an outside grant
Dressler et al., 2019[189]			
Caraballo et al., 2017[190]	• US • Mayo Clinic, Rochester, MN • Funded	• Panel of 50 variants in 13 pharmacogenes • Unknown	• In house (Mayo Clinic Department of Laboratory Medicine and Pathology) • Unknown
Bielinski et al., 2014[191]	• US • Mayo Clinic • The Right Drug, Right Dose, Right Time –Using Genomic Data to Individualize Treatment (RIGHT Protocol) • Funded	• CYP2D6 • Blood	• Both internal and external laboratories (CLIA-certified and CAP accredited Mayo Clinic Clinical Genome Sequencing Laboratory (CGSL) and Personalized Genomics Laboratory (PGL)) • Unknown
Schuh et al., 2019[178]	• US • Mayo Clinic Florida • Not funded	• Multi-gene assay • Buccal swab	• Outsourced • Out of pocket
Ferreri et al., 2014[192]	• US • Single pharmacy in North Carolina • Funded	• CYP2C19 • Buccal swab	• Outsourced, Laboratory Corporation of America (LabCorp) • No cost from patient for the test but with the patient's permission, charges for this visit were billed to insurers when feasible using MTM Current Procedural Terminology
O'Connor et al., 2012[193]			
O'Connor et al., 2012[194]			

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
			(CPT) codes and International Classification of Diseases, 9th revision, codes provided by the prescriber.
Petry et al., 2019[195]	• US • Sanford Health includes 45 hospitals and 289 clinics in nine states with 1300 physcians and 80 specialty areas of medicine • Funded	• Preemptive PGx testing, started with CYP2C19 then expanded to 11 genes later • Blood	• In house laboratory (Sanford Molecular Genetics Laboratory) • Unknown
Christensen et al., 2021[196]			
Hicks et al., 2012[197]	• US • St. Jude PG4KDS • Funded	• 1,936 genomic variants in 225 genes, and is supplemented with a CYP2D6 copy number assay • The initial 2 genes chosen for migration into the EMR were CYP2D6 and TPMT • Blood	• Outsourced • Unknown
Hoffman et al., 2014[198]			
Crews et al., 2011[199]	• US • St. Jude Children's Research Hospital • Funded	• Thiopurine methyltransferase (TPMT) and uridine glucuronosyltransferase 1A1 (UGT1A1), cytochrome P450 2D6 (CYP2D6) • Blood	• In-house • Outside laboratory selected from several reference laboratories that offer pharmacogenetic testing services • Reimbursement was established according to the CPT codes for each test; however, no insurance reimbursement was established for the pharmacist's consults.
Haga et al., 2021[200]	• US • Thirty-six pharmacists at 22 independently-owned community pharmacies across North Carolina • Funded	• Unknown • Buccal swab	• Outsourced, Pathway Genomics • Unknown
Brown-Johnson et al., 2021[201]	• US • Stanford Health Care • Humanoid was implemented in a single academic primary care clinic in the community over an	• Unknown • Saliva	• Unknown • Free

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
	approximate 12-month period · Funded		
Pasternak et al., 2020[202]	· US · Large Academic Health Center · No external funding	· Multiple pharmacogenes · No information on specimen	· Both internal and external laboratories (mostly external) · Unknown
Johnson et al., 2017[203]	· US · Kaiser Permanente Colorado · Funded	· CYP2C19 · Blood · turnaround time 3-5 business days, median turnaround time 5-6 days	· Outsource laboratory (Genelex Laboratory, Seattle, WA) · Unknown
Finkelstein et al., 2016[204]	· US · outpatient clinical practice	· CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, VKORCI · Buccal swab · Turnaround time one week	· Outsource laboratory (GENETWORx Laboratory, LLC, NY) · Unknown
Smith et al., 2019[205]	· US · Pilot in 4 perioperative and 5 outpatient cardiology clinics · Funded	· Reporting genes were CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DPYD, and TPMT · Buccal swab to test 41 genes · Turnaround time one week	· Commercial laboratory · Unknown
Shuldiner et al., 2014[206]	· US · University of Maryland Personalized Anti-platelet Pharmacogenetics Program (PAP3) · Funded	· CYP2C19 · Blood	· In-house, University of Maryland Translational Genomics Laboratory (TGL) · Unknown
O'Donnell et al., 2014[207]	· US · University of Chicago "The 1200 Patients Project" · Funded	· Multigene panel · Blood	· Outsourced, Knight Diagnostic Laboratories, Oregon Health & Science University · Unknown
Goldspiel et al., 2013[208]	· US · National Institutes of Health Clinical Center (NIH CC)	· Abacavir (HLA-B*57:01), allopurinol (HLA- B*58:01), and carbamazepine (HLA-A*31:01, HLA-B*15:02) · Unknown	· In-house · Unknown

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
Strum et al., 2013[209]	• US • Ohio State University Wexner Medical Center , in partnership with the Coriell Personalized Medicine Collaborative (CPMC) • Funded	• CYP2C9, VKORC1, CYP4F2, CYP2C19 • Unknown	• Unknown • Unknown
Bain et al., 2018[210]	• US • A centralized pharmacy in New Jersey that services 15%-20% of PACE participants in 21 states	• CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, VKORC1, SLCO1B1, TPMT, ATM, and F5 • Buccal swab	• Unknownoutside laboratory (CLIA certified Genetrait Laboratories, Columbia, MO) • No cost for testing, fee was billed to PACE organizations by the pharmacy
Schwartz et al., 2017[179]	• US • Elmwood Family Physicians, a private family, primary care practice with 2 locations in New Jersey (Marlton and Tabernacle) • Funded	• CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, VKORC1, SLCO1B1, TPMT, ATM, F2, F5, MTHFR (A1298C), and MTHFR (C677T) • Buccal swab	• Outsource lab (Gene Trait Laboratories, Columbia, MO) • Cost $300
Huddleston et al., 2017[211]	• US • Inova Health System (VA, USA) • Funded, in parts	• Preemptive newborn PGx testing program, seven genes (TPMT, CYP2C9, VKORC1, SLOC1B1, CYP2D6, CYP2C19, CYP3A5) • Buccal swab • TAT for testing was 5.8 ± 2.2 days • TAT for MTM plus service was 11.7 ± 6.2 days	• In-house, hospital campus-based Inova Genomics Laboratory (CAP and CLIA certified) • Free
Gottesman et al., 2013[212]	• US • Mount Sinai Medical Center • CLIPMERGE PGx • Funded	• Clopidogrel (CYP2C19), warfarin (CYP2C9 and VKORC1), simvastatin (SLCO1B1), TCAs (CYP2D6 and CYP2C19) and SSRIs (CYP2D6) • Saliva	• In-house, CLIA-certified Mount Sinai Genetic Testing Laboratory (MGTL) • Unknown
Luczak et al., 2021[213]	• US • A large community-based health system that spans several states (Duluth, MN, Brainerd, MN, and Fargo, ND) • Funded	• 27 distinct genes • Buccal swab • Total turnaround time of 5 days or less	• Outsourced, CLIA-certified laboratory, OneOme, LLC • Free

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
Liko et al., 2021[214]	• US • University of Colorado Hospital (UCH) located at the University of Colorado Anschutz Medical Campus	• 27 genes • Buccal swab	• Outsourced • $500 which was included in the Executive Health Program (EHP) package
Manzi et al., 2016[215]	• US • Boston Children's Hospital	• Initially TPMT and thiopurines then expanded to 225 genes for preemptive genetic testing • Unknown	• Outsourced • Unknown
Dunnenberger et al., 2016[216]	• US • Northshore University HealthSystem pharmacogenomics clinic	• Multigene panel • Buccal sample	• Outsourced • Unknown
Hicks et al., 2016[217]	• US • Cleveland Clinic Health System	• HLA-B*57:01-abacavir, HLA-B*15:02-carbamazepine, and TPMT-thiopurines • Unknown	• Outsourced • Multiple third-party payers reimburse for test costs
Bright et al., 2015[218]	• US • Four community pharmacies in central and northwest Ohio	• Clopidogrel–CYP2C19 • Buccal swab	• Outsourced • Free
Gill et al., 2021[219]	• US • Arkansas Children Hospital • Funded	• Multigene panel • Buccal swab and blood	• In-house molecular pathology laboratory at ACH • Using a blended fixed and variable cost matrix calculation, the total cost to perform the open array pharmacogenomics panel ranges from USD 1195 (1 patient plus 2 controls) to USD 276 (14 patients plus 2 controls) • For billing purposes, each gene on the SNP-based genotyping pharmacogenomics test is paired with the corresponding AMA-approved CPT code
Liu et al., 2021[220]	• US • Vanderbilt University Meidcal Center • PREDICT • Funded	• Multigene panel • Blood	• In-house • Initially free, later transitioned to a billing model including reimbursement by insurance when available

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
Suarez-Kurtz et al., 2020[221]	• Brazil • National Cancer Institute • Three other institutions: ICESP, HACC, and HC-UFRGS • Funded	• DPYD, UGT1A1, TPMT, NUDT15I • Blood or DNA samples • Turnaround time one week	• In-house laboratory at the National Cancer Institute • Unknown
Kim et al., 2019[222]	• Canada • Funded	• CYP2D6, CYP2C19, DPYD • Unknown	• Unknown • Unknown
Papastergiou et al., 2017[223]	• Canada • Two busy urban community pharmacies operating under the brand Shoppers Drug Mart in Toronto, Ontario	• Nine genes (CYP2C9, VKORC1, SLOC1B1, CYP2D6, CYP2C19, CYP3A5, CYP1A2, CYP3A4, OPRM1) • Buccal swab	• Outsourced • Free
Cohn et al., 2021[224]	• Canada • The Hospital for Sick Children in Toronto, Ontario • Funded	• PGx analysis of whole-genome sequencing data and/or multiplex genotyping of 6 pharmacogenes (CYP2C19, CYP2C9, CYP2D6, CYP3A5, VKORC1, and TPMT) • Buccal swab	• Outsourced • Unknown
Breaux et al., 2020[225]	• Canada • Community Pharmacy, British Columbia • Funded	• 592 SNPs • Saliva	• Outsourced • $199 covered by the project budget
Martens et al., 2019[226]	• Netherland • Amsterdam University Medical Centers	• DPYD genotyping and DPD phenotyping • Blood sample	• Unknwon • Unknown
Bank et al., 2019[227]	• Netherland • One academic medical center (Leiden University Medical Center) • Funded	• Preemptive, CYP2C19, CYP2D6, CYP2C9, CYP3A5, DPYD, SLCO1B1, TPMT, and VKORC1 • Saliva • Average turnaround time from drug prescription to returning the results (including time for shipping of the sample to LUMC) was 23.4 ± 8.3 days	• In-house • Free
Thornley et al., 2021[228]	• Netherland • Community Pharmacy • Funded	• 27 genes (111 alleles) • Buccal swab	• Outsourced • Unknown
Lanting et al., 2020[229]	• Netherland • University Medical Center of Groningen • Funded	• Multigene panel of 14 genes • Blood	• In-house • Unknown

Study Author and Year	Settings Funding Information	PGx Information (Type, Genes, Specimen, turnaround time)	Intervention Information (In-house laboratory vs. Outsource laboratory) Cost or Reimbursement
Dunbar et al., 2012[230]	• New Zealand • Funded	• CYP450 • Blood	• Outsource • No cost by Roche Diagnostics
Borobia et al., 2017[177]	• Spain • LaPaz University Hospital • Not funded	• A custom single nucleotide polymorphism (SNP) microarray, which has allowed screening of 180 SNPs associated with drug response (PharmArray) • Mainly peripheral blood cells using Chemagen technology, but for some cases saliva or tissue	• In house • Cost of testing and individual consultation was 216 Euro

4.2.3. Barriers and Facilitators of Genetic Testing Implementation

Barriers and facilitators classified into the 5 domains of CFIR including intervention characteristics, inner settings, outer settings, characteristics of the individuals, and process were displayed in table 2 and table 3, respectively. In the next section, we highlighted these barriers and facilitators.

4.2.3.1. Intervention Characteristics

Besides the description of characteristics of the included studies in the previous section, the majority of these studies provided little to no direct information regarding relative advantage, adaptability, trialability, and complexity of a genetic testing implementation. Arwood et al., 2020 specified that they chose a general internal medicine clinic as a setting because of the existing infrastructure, which indicates that an implementation process can be tailored or adapted based on the available resources.[183] To address the dilemma to choose between blood draw, buccal swab, and saliva, most studies preferred buccal swab because it was convenient to use for younger population and easy to administer.[102,218] This is especially important as some clinic locations may not even have a phlebotomy station to draw blood from patients.[102] Studies did also experience difficulties in patient enrollment including referral process using EHR, identifying patient for referral, and contacting patients.[187,214,216] Cost and reimbursement issues have been mentioned as the most important barrier across all studies.[22,98,102,182,183,186,189,192,193,195,201,206,210,213,214,217-219,221,223,228,230] No accurate information on which insurance providers reimburse for which test makes the situation more complex.[183] Out-of-pocket method was considered as a facilitator and the least complex method, specifically for the health programs that enrolls self-referred individuals.[178,214] Because cost is a major barrier, it was discussed that testing for a single gene instead of testing panel genes could be an option to save money.[183] However, no studies have documented any evidence regarding whether panel genes are better than single gene testing.

The second and third most cited barriers, among all the studies, are the lack of evidence regarding genetic testing utility and frequent updates in these evidences.[98,102,186,188,190,191,196,199,201,204-206,221,225] One

study highlighted the role of PGx steering committee to review the tests offered on a regular basis to be informed about the newest updates.[199] Also, it is recommended that conducting clinical trials to demonstrate clinical efficacy could also be useful to address this barrier.[204] Next, lack of clear guidance on what genes to test, as well as choices between preemptive and reactive testing, was another important barrier to genetic testing implementation.[216] Most studies also mentioned about the long turnaround time which ultimately led to a delayed clinical action.[22,179,184,186,193,199,201,209,213,226,230] Although some prescribers and patients were willing to wait for the results, using rapid point-of-care testing and preemptive testing could be useful to avoid this barrier.[22] Another important barrier across different studies was the difficulty around translation and interpretation of genetic testing results.[22,98,184,201,204,205] Designated team or personnel as well as automated reported system should be present to respond to these issues.[186,215]

4.2.3.2. Inner Settings

Majority of the included studies did describe the structural characteristics of the settings adequately. A brief overview of these settings is already presented in the overall characteristics section above. Nonetheless, little to no information was provided on culture, compatibility, and relative priority. Only Hoffman et al., noted that clinicians in their study had the culture to embrace innovative treatment strategies while Martens et al., considered changing culture as an important factor to implement PGx testing.[198,226] Because real world setting differs from the research environment, implementing a PGx service in a real world setting after testing it in a research setting is a challenge; and as such, it was cited as one of the most important inner setting barriers.[182,185] Sharing critical challenges and their solutions among individual sites, and ultimately conducting feasibility studies were useful to address this barrier.[186,188,209,214] Lack of available training was considered as the most important barrier in this inner setting section.[102,182,187,190,191,201,211,221,229] Different studies had different approaches to address this issue including: incorporating training in genomics in medical school curricula, bringing PGx consultants in the

team, formal education programs, and training pharmacists etc.[98,184,201,205] Problems around clinical decision support (CDS) tools were difficult to address in most cases.[102,186,190,195,204,229] It is important to collaborate with informatics group to create this tool within EHR and regularly revise the alerts based on the feedback.[187] A CDS system that can alert at the time of medication order entry, provide access to pharmacists consultation notes, and account for phenoconversion would be highly preferrable to the clinicians.[22,102,205]

Another important but easily addressable barrier was communication issues such as conflicts, and disagreements between various stakeholders.[98,189,190,200,223,225,226,229] Several solutions were discussed to improve communication between the stakeholders including creating partnerships through a decentralized model, using interactive apps, allowing pharmacists attendance at provider meetings, and having a method to trace communications etc.[102,183,192,204] A substantial number of studies highlighted the importance of the leadership group, and role of key stakeholders including clinicians, pharmacists, and patients.[102,180,186-189,198,205,206,211,217] Although patient population was chosen based on the settings and availability, there was a lack of clear guidance on who to test.[22,189,207,216] In addition, lack of nomenclature was another important barrier to implement genetic testing in practice.[190,215,217,229] Creating own problem list nomenclature could be an option to overcome this barrier.[198]

Most studies discussed inner settings in terms of available resources to implement PGx services such as resources to select genes, EPIC electronic health record, IGNITE network SPARK toolbox, and institutional support.[180,181,195,205] The required infrastructure to implement genetic testing in any healthcare setting is pivotal because there are technical hurdles to integrate PGx service with other pharmacy operations.[98,181,182,189,190,192,193,195,204,206,207,217] Entering genotype results as discrete data could be appropriate to integrate genetic information into EHR.[102,186] Alternatively, results can be scanned as pdf to keep the process easier.[195,215] Since genetic testing results are sensitive to share, privacy, and ethical concerns were considered as important barriers.[179,203,206,211] This can be avoided using HIPAA compliant

server or cloud, an online account for the research team to share results and using secure electronic communications etc.[178,179,192-194,204,210,226] Identifying clear roles and responsibilities in advance for all relevant stakeholders prior to project implementation was mentioned as a solution to the unclear allocation of responsibilities barrier.[179,226]

4.2.3.3. Outer Settings

Overall, a brief description of the enrolled patients was provided in most of the studies. Brown-Johnson et al., recommended patients with multiple medications or those preparing for an operation to undergo PGx testing because of their high-risk nature.[201] Fishe et al., mentioned that COVID-19 pandemic halted the patient enrollment process.[185] It is noteworthy that most studies did not provide any information about patient needs and resources, peer pressure, cosmopolitanism, external policy, and incentives. Only Dunnenberger et al., mentioned that the idea for the pharmacogenomics clinic was inspired by several requests to the medical center by patients and clinicians interested in PGx testing suggesting the patients needed the service .[216] With regards to lack of guidance regarding reimbursement, researchers suggest that there should be clear criteria for billing and documentation by the payers to justify whether a certain test will be reimbursed.[98] More clinical outcomes and cost-effectiveness data are required to support reimbursement.[102] Lack of knowledge about genetic testing among patients was described as another important barrier.[22] Designed flyers and brochures could be on display in patient exam rooms for advertisement purposes.[183] The fact that pharmacists were not recognized as major health care provider is a major barrier.[193] To address this, the Pharmacy Practice Act in North Carolina allowed the pharmacists to serve as a provider extender so that they could order the lab tests.[193] Besides, potential insurance discrimination was mentioned as another barrier to PGx implementation.[211] Testing from outside laboratories was a major barrier since it delays turnaround time. Working collaboratively with external

partners and learning from published experiences of early implementers were considered as important facilitators to implement genetic testing in any healthcare setting.

4.2.3.4. Characteristics of Individuals

In some cases, prescribers and pharmacists were not familiar with PGx-informed prescription i.e., genetic test results interpretation and understanding PGx recommendations.[102,189,214,221] Offering free genetic testing to physicians to personally experience it could be a captivating strategy for them to become familiar with PGx-informed prescription.[183] Doing so will address one of the critical factors which limited the implementation process due to the lack of knowledge, skills, acceptance, and interest among the relevant stakeholders such as prescribers, pharmacists, nurses, and genetic counselors.[22,98,179,186,187,189,190,193,195,199-201,204,206,209,210,216,223,228,229] Different education strategies for different stakeholders such as case-based discussions, long term education plans, and routine meetings with formal competencies were considered as facilitators to address this barrier.[22,196,198,216] Researchers from the University of Florida Health PMP program experienced that providers from different specialties required diverse education needs.[181] Lack of trained personnel was considered as one of the most important barriers in this domain.[221] It is beneficial when trainers of similar educational background and expertise deliver the presentation such as pharmacists train pharmacists and doctors train doctors.[206] It was evident that pharmacists could play a vital role in improving communication through one-on-one telephone consultations, electronically sending recommendations to clinician's office, and taking the initiative to facilitate the implementation process.[178,210] Utilizing pharmacists as a drug expert to guide PGx prescribing and ensure adherence to implementation were suggested by several early PGx service adopters.[186,225] With regards to clinicians, several steps were suggested to reduce their workload such as providing educational materials for every new gene-drug pair implementation, sending user-friendly PDF test results, and conducting focus groups with them to understand their need.[183,190,191,198]

4.2.3.5. Process

In general, the included studies rarely described the process of implementation. Having PGx champions was considered as an important facilitator to implement PGx service across the studies.[102,186,188,190,195,214] Limited program evaluation data, specifically struggling with both measuring and accessing outcomes data, was mentioned as an important barrier to implement PGx services.[22,187] Quality control procedures such as patient satisfaction surveys, and inclusion of dedicated research component like METRICS should be implemented to address this barrier.[196,211] Barriers such as unexpected changes during the implementation process may not be addressed until sufficient exposure to a volume of patients occurs.[222]

Table 17. Barriers to Implement Genetic Testing Using Consolidated Framework for Implementation Research

Domains	Barriers
Intervention characteristics	• Complex process for multi gene panel[187] • Complex process for multi morbid patients[187] • CYP2D6 is a complex gene to interpret[102] • Different clinical situation for different drug-gene pairs[208] • Difficulties in choosing sampling method[22,182,186,230] • Difficulty in referral process using EHR, inconvenience and challenge of identifying patient for referral, difficult to locate or contact patients, maintaining steady referral rate[183,187,214,216] • Higher cost and reimbursement issues[22,98,102,182,183,186,189,192,193,195,201,206,210,213,214,217-219,221,223,228,230] • Lack of clear guidance on what genes to test[216] • Lack of evidence, unclear evidence, or frequent updates in evidence[98,102,186,188,190,191,196,199,201,204-206,221,225] • Long turnaround time[22,179,184,186,193,199,201,209,213,226,230] • Medication and family history-taking is burdensome[216] • Translation and interpretation of results are difficult[22,98,184,201,204,205]
Inner settings	• Adopting in a real-world organization is different from research environment[182,185] • Available training does not fulfill needs or lack of training[102,182,187,190,191,201,211,221,229] • CDS issues such as alert fatigue and inclusion of both inpatient and outpatient setting required two distinct CDS approval[102,186,190,195,204,229] • Communication problems, conflicts, or disagreements[98,189,190,200,223,225,226,229] • Integrating genetic information into EHR is difficult[110,179,186,187,195,201,204,206,210,213,217] • Lack of clear guidance on who to test[22,189,207,216] • Lack of nomenclature that systematically conveys pharmacogenomic results and standardization, absence of standardized reporting format[190,215,217,229] • Limited access to medical records[192,210] • Limited access to genetic counselor[201] • Other infrastructure issues, technical hurdles for result storage and review[98,181,182,189,190,192,193,195,204,206,207,217] • Privacy or consent, ethical concerns[179,203,206,211] • Unclear allocation of responsibilities between healthcare practitioners, no mention of key stakeholders[210,229]

Domains	Barriers
Outer setting	• Covid pandemic halted enrollment[185] • Lack of clear guidance regarding reimbursements[98] • Lack of knowledge, and perception about PGx among the patients[22] • Pharmacists are not recognized as major health care provider[193] • Potential insurance discrimination[211] • No control when testing from outside laboratories[181,186,190,191,195,206] • Wide range of clinical specialties translated to diverse provider education needs[181]
Characteristics of individuals	• Lack of familiarity with PGx-informed prescription[102,189,214,221] • Lack of knowledge, skills, acceptance and interest among the prescribers, genetic counselors, and pharmacists[22,98,179,186,187,189,190,193,195,199-201,204,206,209,210,216,223,228,229] • Lack of trained personnel[221] • Different physician had different approaches for results interpretation and sharing[189]
Process	• Challenges in measuring outcomes including extraction of relevant adverse events and cost data from EHR with regards to evaluation[187] • Limited program evaluation results available[22] • Unexpected changes during the implementation process[222]

Table 18. Solutions to the Identified Barriers to Implement Genetic Testing Using Consolidated Framework for Implementation Research

CFIR domains	Solutions to the Identified Barriers
Intervention characteristics	**Complex process for multigene panel** · Could test for a single gene instead of panel and it also saves money.[183] · Panel validation i.e., repeat testing of reference samples, analysis, and refinement of the panel is important because it ensures that only relevant genes are being tested.[207] **CYP2D6 is a complex gene to interpret** · CYP2D6 genotype expertise important for establishing genotyping procedures and interpreting results.[102] **Different clinical situation for different drug-gene pairs** · Prescribers recognized the need for additional information about PGx and welcomed eLearning and specialty-specific educational sessions as alternative means of education.[219] **Difficulties in choosing sampling method** · DNA sampling requirements involved only a buccal swab, which was discussed and demonstrated in the one-hour training, and laboratory testing was handled off-site.[218] · Offering noninvasive genetic sample collections is key for younger populations.[22,102] · Blood draws do not seem problematic in adults, but it may not be the most convenient option as not all clinic locations have phlebotomy stations.[102] **Difficulty in referral process using EHR, inconvenience and challenge of identifying patient for referral and adding same day PGx visit, difficult to locate or contact patients** · Ordering forms were straightforward and easy to complete[230] · A referral order can be built in the EHR[216] · Drafted a patient result letter with a brief explanation of the results in laymen's terms and suggested actions, e.g., that the patient discusses their results with their current healthcare practitioners and share results with any new ones[229] **Higher cost and reimbursement issues** · Self-pay is the least complex method to obtain payment for services.[178] · Executive health programs are a good venue for implementing PGx because enrolled patients are receptive to new innovations, and cost is not a barrier given that these patients are accustomed to self-paying for associated services.[214] · PGx test under $100 would be a great strategy to get the prescriber on board with it[189] · May require the patient to pay out-of-pocket and then request reimbursement from their insurance carrier, while patients can pay out-of-pocket on a per minute, per half hour, or per service basis. Billing platforms such as MirixaPro and Outcomes Pharmaceutical Health Care may be useful for billing claims and are beneficial if the pharmacy is already using these platforms to deliver MTM services.[193] · Some PGx clinics with MTM services collaborated with another provider to use incident-to billing code for reimbursing pharmacist services.[214] **Lack of clear guidance on what genes to test** · Focused screening of certain clinically relevant genes in various ethnic populations.[223] · CPIC provides an excellent set of tools and guidelines to guide clinical implementation.[195]

CFIR domains	Solutions to the Identified Barriers
	Lack of evidence regarding utility, unclear evidence or frequent updates in evidence · Personnel need to stay informed of scientific developments in the field and update reports and decision support as needed.[102] · The Clinical Pharmacogenetics Service steering committee has proved valuable to review the tests offered on a regular basis to be certain the tests remain relevant and useful.[199] · Comprehensive public resource of certified facilities that is maintained and curated by designated academic centers and industry.[204] · More clinical trials providing evidence on clinical efficacy are required.[204] · Need a national consensus between PGx experts and medical societies in charge of the clinical guidelines to widely disseminate standardized PGx knowledge that can be easily accepted by clinicians and quickly implemented in clinical practice.[190] **Long turnaround time** · Rapid point-of-care testing or pre-emptive testing.[209] · Prescribers, patients and parents were willing to wait for results in some settings. [22] · Be performed in a preemptive manner.[224] **Translation and interpretation of results are difficult** · A designated person or team to respond to results improves efficiency of therapy changes.[186] · Automated reporting saved genetic counselor time by calculating diplotypes and assembling report content, while also ensuring consistent and reproducible reporting.[215]
Inner settings	**Adopting in a real-world organization is different from research environment** · Individual sites were sharing with one another the critical challenges in implementation of genomics.[116] · Pilot feasibility studies were useful not only to raise awareness, but also to demonstrate that testing may be more feasible and useful[188] **Available training does not fulfill needs or lack of training** · Create PGx champions in each region of the enterprise and engage key stakeholders, specially who are early adopters[195] · Incorporate training in genomics in medical school curricula and encourage continuing medical education (CME) programs[98] · Extensive education and training for pharmacists in PGx as well as genetic counseling training program[196,210] · Educate providers on testing availability, ordering procedure, incorporating data into standard practice, and testing applications to prescribing decisions[102,219] · Designated personnel and electronic CDS are important to assist with integrating genotype results into prescribing decisions.[102] · Principal investigator can conduct training sessions with research coordinators, pediatric ED nurses, and respiratory therapists.[185] **CDS issues such as alert fatigue and inclusion of both inpatient and outpatient setting required two distinct CDS approval** · Need CDS system that assigns phenotype based on drug substrate and accounts for phenoconversion.[102] · Partner with hospital informatics to create clinical decision support tools and solve ongoing

CFIR domains	Solutions to the Identified Barriers
	EHR challenges[186] · Intelligent decision support requires to account simultaneously for multiple drug-gene and drug-drug interactions and assist in medication regimen optimization[204] · Providers may prefer for electronic clinical decision support alerts at the time of medication orde entry and access to pharmacists consultations[205] · "Alert fatigue" should be considered in the design and exclusion criteria are included in the rules to avoid unnecessary repetitive alerts.[191,217] · Adding new CDS to a PGx portfolio was a key strategy for enhancing the clinical impact of a program.[220] **Communication issues between stakeholders, conflicts, or disagreements** · Create partnerships with pharmacists or other clinicians on clinical teams through a decentralized model[102] · Clinical documentation with recommendations could be faxed, mailed, or securely sent to a provider's office and patients[178] · Interactive apps to support patient engagement in medication management and facilitate patient-provider communication[204] · Pharmacists could be readily available to prescribers for one-on-one telephone consultations[210] · Implementing effective PGx requires a partnership among the patient, provider, and the PGx program[220] · Pharmacist attendance at the provider meetings allowed for brief discussion.[183] · Importance of having a method to track communications is important.[192] · Bringing together research and clinical practice by promoting collaborative investigation and decision making[177] **Integrating genetic information into EHR is difficult** · Enter genotype results as discrete data[102] · An ideal solution is a section of the patient's chart for genetic results, and a quick indicator to note if there are results in there[22] · Another workaround is ensuring the prescriber notes in their encounter note that they are ordering a pharmacogenetic test; then, they will review prior to patient's next visit and will know to look for results[22] · A future solution may be found external to the EHR, perhaps with the data generated by genetic testing existing in an ancillary system specifically designed for storing and querying genomic data on demand from the clinician.[190] · External PGx reports could be scanned into the EMR without being added as discrete results therefore not triggering CDS[195] · Just like drug allergy reminders in the EMR, knowledge could be automated into the system to reduce patient risk and maximize drug efficacy[209] · Created electronic interfaces capable of transferring structured results into the EHR but that also allowed for manual data entry when an electronic solution was not available[190] · Aggregating pharmacogenetic test results into a single section of the EMR on a per-patient basis[197] **Lack of clear guidance on who to test** · Prescribers would like electronic CDS to identify potentially appropriate patients to test patients who might clearly benefit, such as those with multiple medications or those preparing for an operation.

CFIR domains	Solutions to the Identified Barriers
	Lack of nomenclature that systematically conveys pharmacogenetic results and standardization, absence of standardized reporting format · Overcome with workarounds and requires advocacy with the National Library of Medicine to adopt SNOMED codes that are adequate for clinical PGx use[215] · Used extensive translation tables to standardize the phenotypical interpretation of the PGx test results[190] · Because current vocabularies widely used in EHRs (e.g., SNOMED) do not adequately differentiate various phenotypes for priority (high-risk) results, could create own problem list nomenclature[198] **Limited access to EHR for pharmacists** · Pharmacogenetic data can be entered as a message that would make this information available to the pharmacist during the drug utilization review process at each dispensing. Pharmacists can also enter a message in this field stating the patient had been offered the test so they will not inadvertently receive the test again.[193] **Limited access to genetic test including telehealth** · Offering the sale of genomic kits in pharmacies and having the consultation conducted by specially trained pharmacists[223] **Other infrastructure issues, technical hurdles for result storage and review** · Integrate this PGx service with other pharmacy operations[183] · Infrastructure must include not only electronic health record (EHR) systems that have accessible locations for ordering genomic tests, but also CDS tools that reduce the time and burden of finding and interpreting genomic information[98] · Informatics team worked within the existing Lab Information System (LIS) and EHR infrastructure[182] · The financial support allowed to establish a laboratory and informatics pipeline appropriate for genetic testing at a large scale and create education programs and CDS to support health care providers without specialized training in genetics.[196] · An active clinical research program can facilitate the rapid development of the infrastructure and protocols[211] · Requires both initial and ongoing investments in the laboratory and informatics infrastructure.[220] **Privacy or consent, ethical concerns** · PGx laboratory results could be provided electronically through a secure server or cloud or printed to give directly to patients.[178] · An online account for the pharmacogenetics research team was created with the lab company to ensure that all CPP-ordered lab results were delivered and accessible only to study personnel.[193] · Communicated results and consultations with prescribers directly by transmitting documents through secure HIPAA compliant servers and indirectly by uploading documents to participants pharmacy records[210] · Used secure electronic communication to exchange consult information[179] **Unclear allocation of responsibilities between healthcare practitioners, no mention of key stakeholders** · Clear roles and responsibilities should be defined early[226]

Outer setting	**Cosmopolitanism and External Policy Facilitators** • IGNITE investigators were working collaboratively with external partners and IGNITE affiliate members to develop real-world, scalable solutions to these challenges that are informed by a broad sampling of clinical practice settings.[116] • Research team had been involved in the provision of more than 50 genomic counseling sessions gaining 'real world' experience within the setting of an academic medical center[209] • Learn from published experiences of early implementers, domain expert groups (CPIC)[186] **Lack of clear guidance regarding reimbursements** • Clear criteria for evidence requirements billing and documentation by the payers are required to justify whether a certain test will be reimbursed[98] • Clinical outcomes and cost-effectiveness data may support reimbursement and additional stakeholder buy-in.[102] **Pharmacists are not recognized as major health care provider** • Integrating pharmacists as the drug experts to guide PGx prescribing, creating standardized reporting guidelines, and educating clinicians promises to improve the reliability of PGx dosing[225] • Integrate clinical pharmacists as well as community pharmacists to ensure adherence to the implementation algorithm and appropriate follow-up[186] • The Pharmacy Practice Act in North Carolina defines the opportunity for pharmacists to serve as a provider extender, or Clinical Pharmacist Practitioner (CPP). A CPP can order lab tests under collaborative practice agreement. Such opportunities should be available in other states as well.[193]
Characteristics of individuals	**Lack of familiarity with PGx-informed prescription** • Prior experience with other innovative services can help.[180] • Personally genetic experience, offering free genetic testing to physicians.[183,228] • Supplementing automated CDS with an opportunity for front line clinicians to consult physicians with expertise in pharmacogenomics.[187] **Lack of knowledge, skills, acceptance and interest among the prescribers and pharmacists** • Case-based education for prescribers[22,216] • Different education strategies and educational programs addressing research advances, treatment guidelines, and related liability laws are ideal topics for physicians, nurses, and pharmacists already in practice[98] • Identify a physician champion and engage key stakeholders[102,186,188] • Giving physicians and patients the opportunity to experience PGx testing should not only help with familiarity and application, it should also lead to a better understanding of the optimal infrastructure needed to deliver PGx guided care for individual practices and health systems.[188] • Prescribers willing to order genetic test and participants willing to do test.[22] • Genetics education over a 2-year period was mandatory for all physicians and advanced practice providers.[196] • Designed flyers and brochures to display in patient exam rooms to advertise the availability of the service along with common medications impacted by genes[183] • Study presentations and announcements were presented in multiple forums (lectures and meetings) to all ED physicians and staff[185] • Identified key clinicians who played a critical role in the education of their colleagues and in advocacy of the project[187]

	· In some cases, prescriber acceptance was exceptional. No prescribers outright rejected pharmacogenomics recommendations.[192] · All pharmacists are provided with education material and tested on their ability to perform basic interpretation of a phenotype with corresponding drug-specific dosing recommendations.[198] · Pharmacist education on new gene/drug pairs is provided at routine department meetings before formal competencies are assigned.[198] · The community and hospital pharmacists wanted more education about PGx for themselves and pharmacy staff.[229] **Lack of trained personnel** · PGx consultants can serve as an expert resource for clinical consultants, routine questions, and education delivery[205] · Most effective when trainers of similar training background to the audience deliver the presentations[206] · Many pharmacists may already have had experience in providing the foundational MTM, so training associated with patient and prescriber communication could be very minimal[218] · Since PGx can be quickly related to mechanisms of drug interactions, the learning curve for pharmacists was minimal[218] **Physicians' working load** · Unstructured text reports, usually user-friendly PDF files, have been the preferred way to report PGx test results to clinicians.[190] · Conducting focus groups with clinicians to better understand the types of education resources and modes they prefer and would find most beneficial in their integration of pre-emptive PGx into their clinical practice[191] · With every new gene/drug pair implementation, clinicians are provided educational material through various methods (e.g., email, newsletter, webpage, formulary, and routine presentation) to allow them to learn how to use genetic information when prescribing.[198]
Process	**Challenges in measuring outcomes including extraction of relevant adverse events and cost data from EHR with regards to evaluation** · The inclusion of a dedicated research component (METRICS) to explore the impact of integrating genetic testing into general clinical practice by collecting patient reported outcomes.[196] **Limited program evaluation results are available** · Quality control procedures are important for ensuring electronic CDS maintained with EHR updates[102] · Conduct patient satisfaction surveys[177,211] **Unexpected changes during the implementation process** · Sufficient exposure to a volume of patients with similar underlying conditions are required[222]

4.3. Aim 3 Results

Specific Aim 3: To assess the awareness, perceptions, and preferences toward genetic testing among the United States general public, and how this may vary by racial-ethnic group and rural-urban status.

In this section, we will first report on respondents' characteristics and their health literacy and numeracy. Next, respondents' awareness and preferences related to various aspects of genetic testing will be reported. Finally, we will report the findings regarding the perception towards genetic testing across different diseases. For all the survey questions, differences across racial/ethnicity and rurality groups were assessed and presented in sequence.

4.3.1. Demographic Characteristics

A total of 1,600 people participated in this survey across the United States. Data was collected over a period of 5 weeks from December 20, 2021, to January 24, 2022. The survey completion time ranged from 5 to 1,336 minutes, with a median duration of 22 minutes. Demographic characteristics are summarized in the table 1 below. The mean age of participating respondents was 53 (SD = 16.42). Overall, more females (56.38%) completed the survey than males (43.63%). Although this survey intended to include a quarter of each of the four racial and ethnic groups, it was difficult to recruit non-Hispanic Asian population because the Asian alone population accounted for only 6% of all people living in the US. Ultimately, 34% non-Hispanic White, 26% non-Hispanic Black, 26% Hispanic or Latino, and 15% non-Hispanic Asian responded to this survey. The age distribution of the respondents to this survey closely matched with the expected quota. That is, around 17% of the respondents were 18 to 35 years old and 33% were older than 65 years old. Half of the respondents were expected to be recruited from

rural areas. But this study was only able to recruit 33% of its participants from rural areas. Around 39% of the respondents were from suburban and the rest were from urban areas.

More than three quarters of the respondents had at least some college level educational background. Majority of the respondents were from South (43%), followed by West (24%). A little over half of the respondents (54%) used mobile phone to complete the survey while about 38% used desktop or laptop (38%). About 31% respondents reported being current smokers while 5% said they occasionally smoked. Medicare and employer sponsored insurance were ranked the highest, 36% each, when asked about the type of insurance they use. Forty percent of the respondents had high blood pressure and a quarter of the total respondents said they had anxiety and depression. A substantial portion of the respondents said they had chronic pain (17%) and/or diabetes (16%).

Table 19: Demographic Characteristics, N = 1600

Characteristics	Frequency, N (%)
Sex	
Male	698 (43.63%)
Female	902 (56.38%)
Race/ethnicity	
Non-Hispanic Black or African American	411 (25.69%)
Non-Hispanic White	545 (34.06%)
Non-Hispanic Asian	232 (14.50%)
Hispanic or Latino	412 (25.75%)
Age	
18-34 years	276 (17.25%)
35-49	332 (20.75%)
50-64	470 (29.38%)
65-74	351 (21.94%)
75+	171 (10.69%)
Rurality	
Rural	520 (32.50%)
Suburban	629 (39.31%)
Urban	451 (28.19%)
Annual household income level	
<$20,000	229 (14.31%)
$20,000-$49,999	442 (27.63%)
$50,000-$74,999	290 (18.13%)
$75,000-$99,999	195 (12.19%)
$100,000-$199,999	344 (21.50%)
>$200,000	100 (6.25%)

Education level	
No high school diplomas	35 (2.19%)
High school diploma or GED	314 (19.63%)
Some college	500 (31.25%)
Bachelor's degree	447 (27.94%)
Post-Baccalaureate Degree	304 (19.00%)
Regions	
South	683 (42.69%)
West	376 (23.50%)
Northeast	289 (18.06%)
Midwest	252 (15.75%)
Devices Used	
Mobile phone	858 (53.63%)
Desktop or Laptop	610 (38.13%)
Tablet	130 (8.13%)
Other	2 (0.13%)
Currently Smoking or Vaping	
Yes	495 (30.94%)
No	1028 (64.25%)
Occasionally	77 (4.81%)
Insurance*	
Medicare	583 (36.43%)
Employer sponsored insurance	570 (35.63%)
Medicaid	262 (16.38%)
Individual Private Insurance	224 (14.00%)
Tricare - VA	66 (4.13%)
Tribal Health	7 (0.44%)
Others	22 (1.38%)
No Insurance	83 (5.19%)

Diseases*	
High blood pressure	645 (40.31%)
Anxiety	427 (26.69%)
Depression	419 (26.19%)
Chronic pain	272 (17.00%)
Diabetes	252 (15.75%)
Cancer	130 (8.13%)
Heart disease	100 (6.25%)
Macular degeneration	53 (3.31%)
Chronic kidney disease	47 (2.94%)
Epilepsy	29 (1.81%)
Schizophrenia	19 (1.19%)
Huntington's disease	14 (0.88%)
Alzheimer's	13 (0.81%)
Parkinson's	11 (0.69%)
None of these	468 (29.25%)

* Respondents may choose more than one response.

4.3.2. Health Literacy and Numeracy

We measured health literacy and numeracy by asking the participants to rate their confidence in filling out medical forms by themselves. The majority of the respondents (81%) were either extremely or quite a bit confident in filling out medical forms by themselves (Figure 1). Less than 2% of the respondents said that they were not at all confident in filling out any medical forms alone.

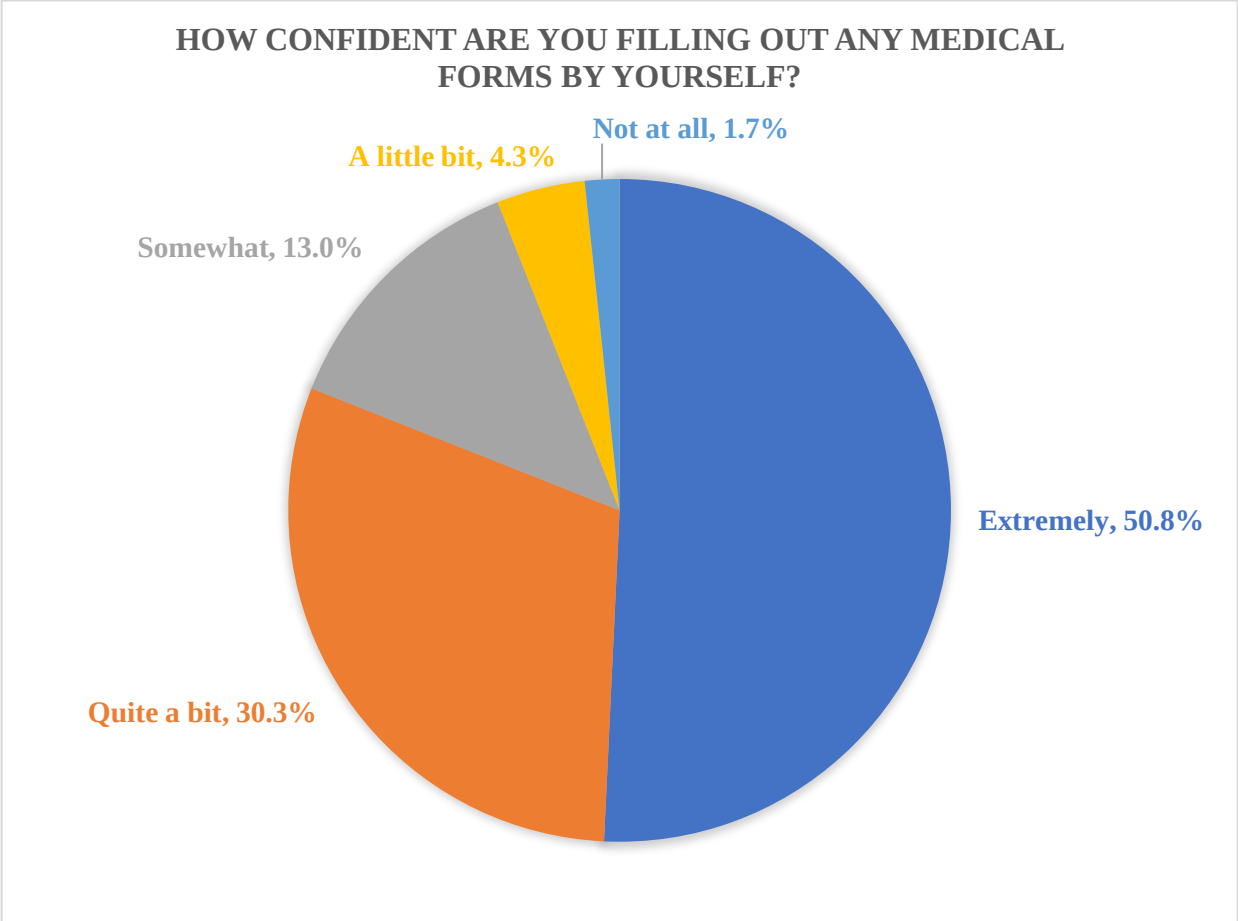


Figure 14: Percentage of Respondent's Confidence in Filling Out Medical Forms Independently, n=1600

4.3.3. Awareness

4.3.3.1. Awareness regarding different types of genetic testing

When asked about which types of genetic tests they have heard of, the majority of the respondents chose ancestry testing (n = 1384, 87%) and genetic health risk testing (n = 1100, 69%). A fair portion of them also have heard of high-risk cancer testing (n = 662, 41%). Results are presented in Figure 2. When stratified by race-ethnicity and rurality, no differences were observed across different groups for ancestry testing, genetic health risk testing and high-risk cancer testing (all P > 0.05).

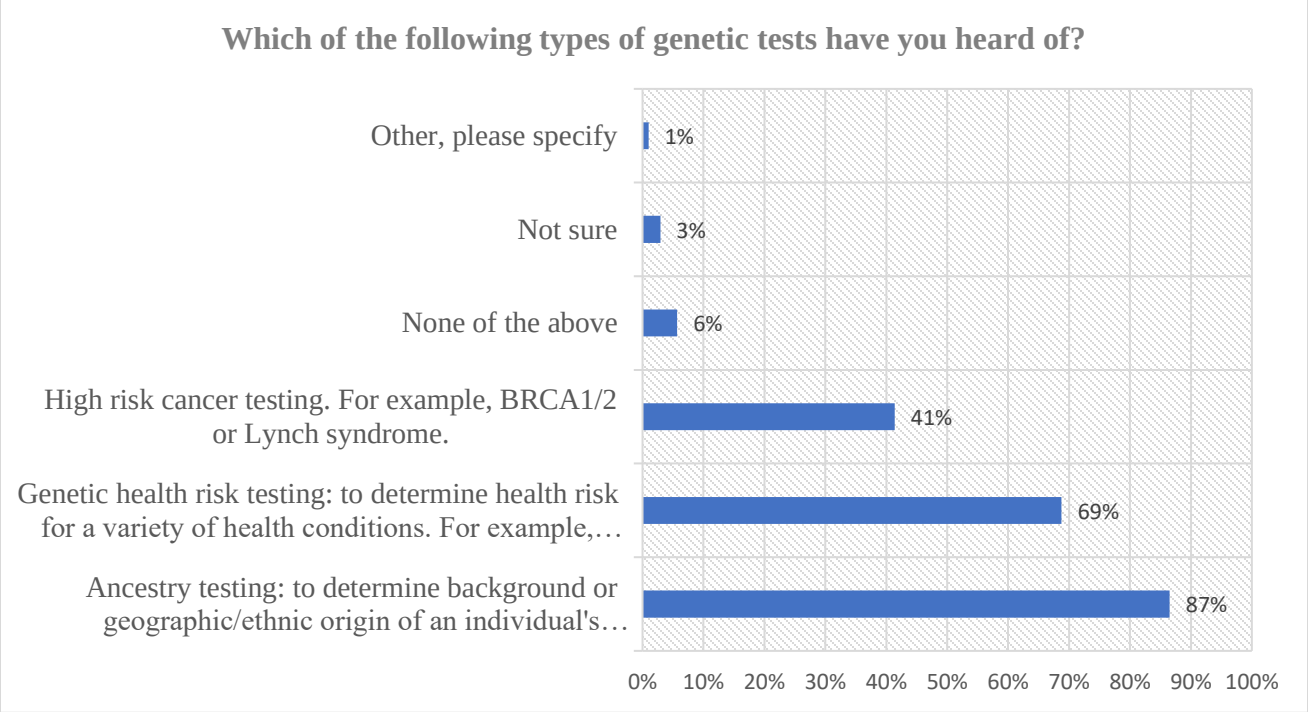


Figure 15: Percentage of Respondents Who Have Heard About Different Types of Genetic Testing, n=1600

4.3.3.2. Awareness regarding gene inheritance

Respondents had different thoughts regarding the extent to which inherited genes could be responsible for different types of diseases (Chi-square, $P < 0.0001$). Around 36% and 33% of the respondents thought that inherited genes may be a little or not at all responsible for obesity and mental health, respectively (Figure 3). In contrast, only 20% to 23% respondents thought of this same way for cancer, heart disease, and diabetes. When stratified by race and ethnicity, significantly more Hispanics ($P < 0.05$) thought that inherited genes are not responsible for cancer and heart disease compared to Whites (10% vs. 5% and 8% vs. 5% respectively). However, for mental health, significantly ($P = 0.001$) higher percentage of Whites thought inherited genes are not responsible compared to Hispanics (12% vs. 8%). No differences were observed when stratified by rurality (all $P > 0.05$). Table 2 provides the percentages of respondents who thought inherited genes are responsible for each of these diseases by rurality, race and ethnicity.

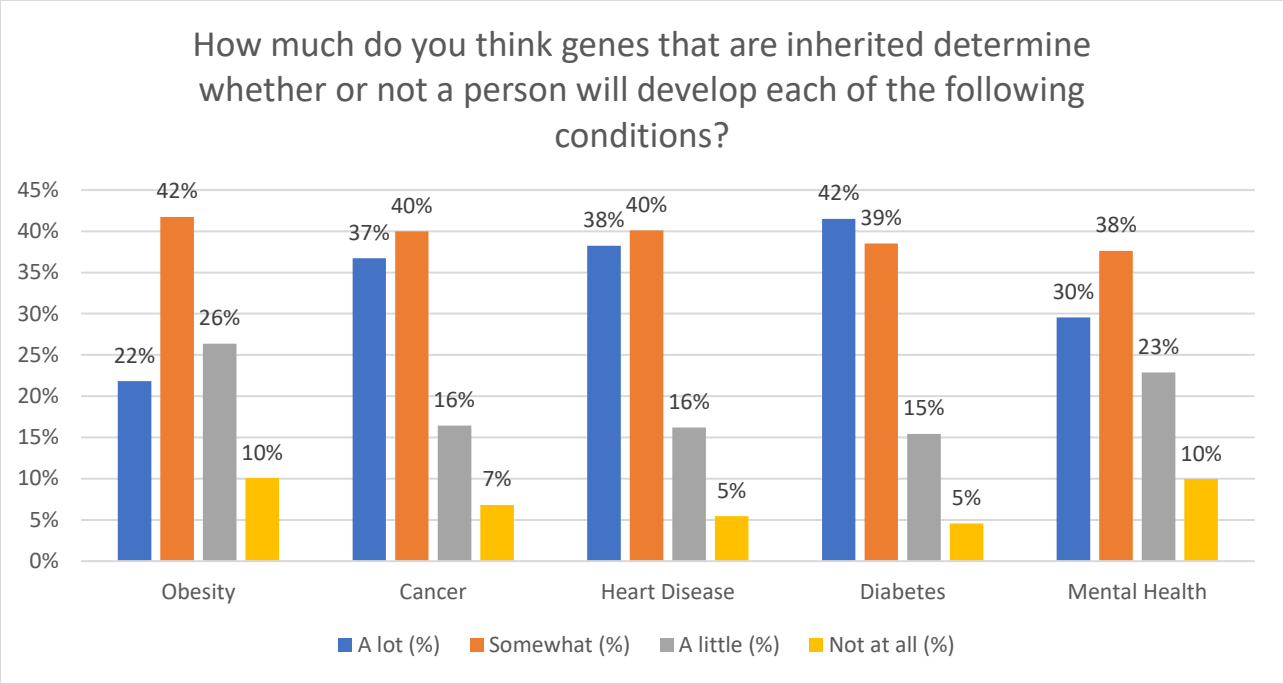


Figure 16: Percentage of Respondents Who Thought Inherited Genes Are Responsible for Different Diseases, n=1600

Table 20: Percentage of Respondents Who Thought Inherited Genes Are Responsible for Different Diseases by Race-Ethnicity and Rurality, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Diseases	**Impact of genes on diseases**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Obesity	**A lot**	121 (22.2%)	96 (23.4%)	39 (16.8%)	93 (22.6%)	P = 0.08	123 (23.7%)	226 (20.9%)	P = 0.13
	Somewhat	227 (41.7%)	181 (44.0%)	103 (44.4%)	157 (38.1%)		225 (43.3%)	443 (41.0%)	
	A little	152 (27.9%)	109 (26.5%)	70 (30.2%)	109 (26.5%)		118 (22.7%)	304 (28.1%)	
	Not at all	45 (8.3%)	43 (10.5%)	20 (8.6%)	53 (12.9%)		54 (10.4%)	107 (9.9%)	
Cancer	**A lot**	185 (33.9%)	164 (39.9%)	78 (33.6%)	161 (39.1%)	**P = 0.01**	193 (37.1%)	395 (36.6%)	P = 0.81
	Somewhat	236 (43.3%)	155 (37.7%)	105 (45.3%)	144 (35.0%)		208 (40.0%)	432 (40.0%)	
	A little	97 (17.8%)	67 (16.3%)	34 (14.7%)	65 (15.8%)		88 (16.9%)	175 (16.2%)	
	Not at all	27 (5.0%)	25 (6.1%)	15 (6.5%)	42 (10.2%)		31 (6.0%)	78 (7.2%)	

Table 20 (continued): Percentage of Respondents Who Thought Inherited Genes Are Responsible for Different Diseases by Race-Ethnicity and Rurality, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Diseases	**Impact of genes on diseases**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Heart Disease	**A lot**	220 (40.4%)	166 (40.4%)	67 (28.9%)	159 (38.6%)	**P = 0.02**	205 (39.4%)	407 (37.7%)	P = 0.25
	Somewhat	217 (39.8%)	168 (40.9%)	109 (47.0%)	148 (35.9%)		213 (41.0%)	429 (39.7%)	
	A little	85 (15.6%)	57 (13.9%)	43 (18.5%)	74 (18.0%)		82 (15.8%)	177 (16.4%)	
	Not at all	23 (4.2%)	20 (4.9%)	13 (5.6%)	31 (7.5%)		20 (3.9%)	67 (6.2%)	
Diabetes	**A lot**	226 (41.5 %)	185 (45.0%)	82 (35.3%)	171 (41.5%)	P = 0.27	219 (42.1%)	445 (41.2%)	P = 0.09
	Somewhat	206 (37.8%)	151 (36.7%)	100 (43.1%)	159 (38.6%)		191 (36.7%)	425 (39.4%)	
	A little	90 (16.5%)	61 (14.8%)	40 (17.2%)	56 (13.6%)		93 (17.9%)	154 (14.3%)	
	Not at all	23 (4.2%)	14 (3.4%)	10 (4.3%)	26 (26.3%)		17 (3.3%)	56 (5.2%)	

Table 20 (continued): Percentage of Respondents Who Thought Inherited Genes Are Responsible for Different Diseases by Race-Ethnicity and Rurality, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Diseases	**Impact of genes on diseases**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Mental Health	**A lot**	136 (25.0%)	137 (33.3%)	51 (22.0%)	149 (36.2%)	**P = 0.001**	162 (32.80%)	311 (28.8%)	P = 0.71
	Somewhat	216 (39.6%)	150 (36.5%)	87 (37.5%)	149 (36.2%)		195 (28.82%)	407 (37.7%)	
	A little	130 (23.9%)	89 (21.7%)	67 (28.9%)	80 (19.4%)		116 (29.31%)	250 (23.1%)	
	Not at al	63 (11.6%)	35 (8.5%)	27 (11.6%)	34 (8.3%)		47 (29.31%)	112 (10.4%)	

4.3.3.3. Awareness regarding facts about genetic testing

In addition, to assess respondents' awareness of the impact of genetic testing, we asked a series of true or false questions when true responses indicated correct awareness. Majority of the respondents were correct on the statements that says genetic testing can help in identifying risk of disease as well as prenatal risks, and diseases can pass from parents to children. However, half of the respondents were not aware of the impact of genetic testing to identify medication side effects in advance or choosing the right medication (Figure 4). More than sixty percent of the respondents did not know the role of genetic testing in correcting medication dosages. When these three statements were stratified based on rurality, race and ethnicity, significant differences were observed (Table 3). For example, significantly less African Americans thought that genetic test can identify side effects in advance, correct dosages, or select the best medication for them compared to other racial and ethnic counterparts (all $P < 0.01$). Besides, significantly fewer rural residents thought that genetic tests can identify adverse events or correct the dosages compared to urban respondents ($P < 0.01$). However, no significant difference was observed on selecting the best medication statement for rurality.

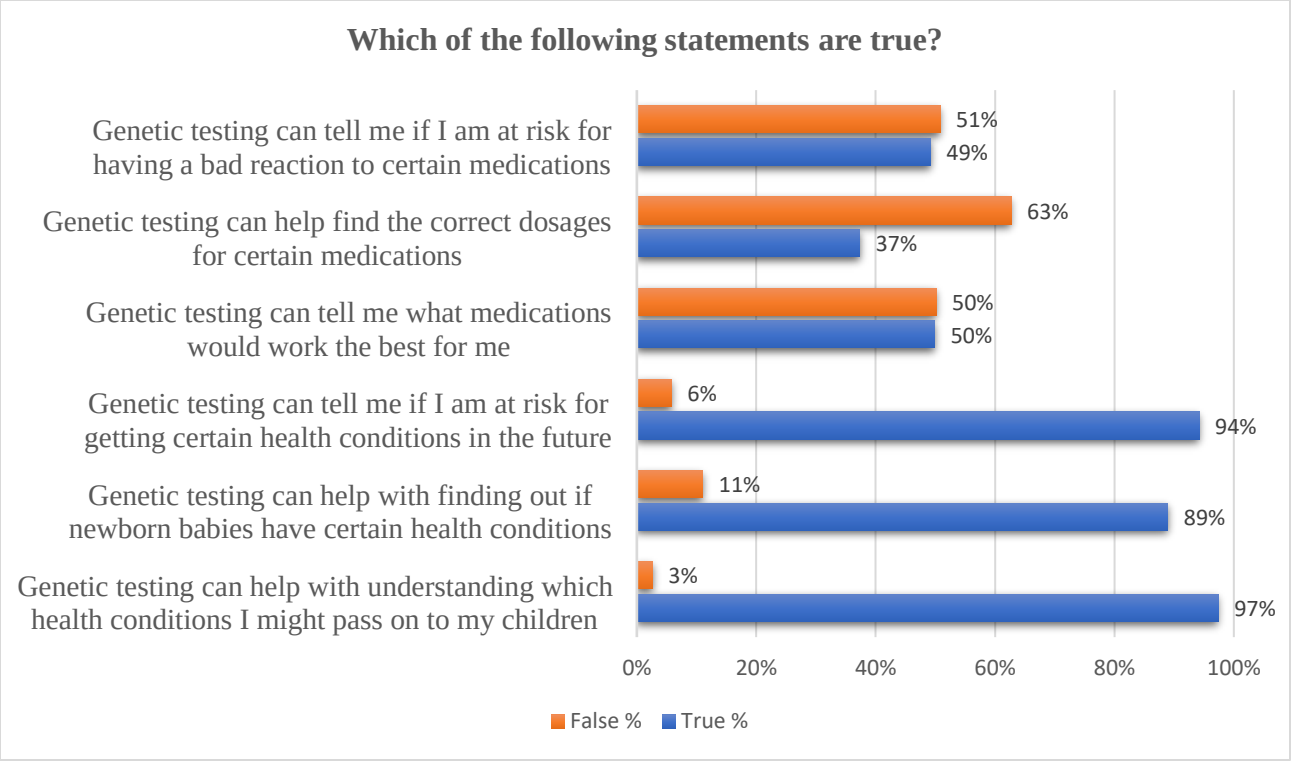


Figure 17: Percentage of Respondents Who Identified True Genetic Testing Facts, n=1600

Table 21: Percentage of Respondents Who Identified True Genetic Testing Facts by Race-Ethnicity and Rurality, n=1600

		Race - Ethnicity n (%)					Rurality n (%)		
Statements	**Response**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Genetic testing can tell me if I am at risk for having a bad reaction to certain medications	**True**	258 (47.3%)	173 (42.1%)	130 (56.0%)	226 (54.8%)	**P < 0.001**	230 (44.2%)	557 (51.6%)	**P = 0.006**
	False	287 (52.7%)	238 (57.9%)	102 (44.0%)	186 (45.2%)		290 (55.8%)	523 (48.4%)	
Genetic testing can help find the correct dosages for certain medications	**True**	197 (36.2%)	130 (31.6%)	102 (44.0%)	168 (40.8%)	**P = 0.006**	169 (32.5%)	428 (39.6%)	**P = 0.006**
	False	348 (63.9%)	281 (68.4%)	130 (56.0%)	244 (59.2%)		351 (67.5%)	652 (60.4%)	
Genetic testing can tell me what medications would work the best for me	**True**	258 (52.5%)	169 (41.1%)	132 (56.9%)	211 (51.2%)	**P < 0.001**	244 (46.9%)	554 (51.3%)	P = 0.10
	False	287 (47.5%)	242 (58.9%)	100 (43.1%)	201 (48.8%)		276 (53.1%)	526 (48.7%)	

4.3.3.4. Pharmacogenetic testing

More than half of the patients never heard about either preemptive or reactive testing (Table 4). Around a third of the Black respondents heard about these two testing in comparison to 42.2% Asian, 45.5% White, and 49.8% Hispanic (P < 0.0001). Not surprisingly, significantly more urban respondents heard about these testing compared to rural and suburban population (Urban 47.0% vs. Rural 34.4%, P < 0.0001).

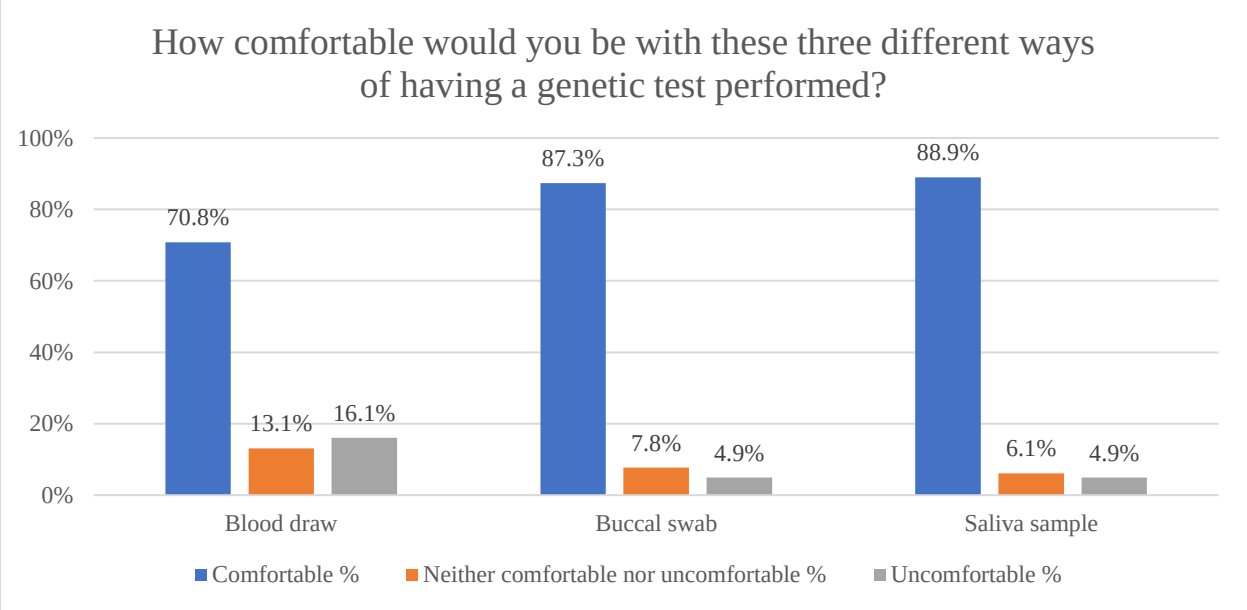
Table 22: Percentage of Respondents Who Had Heard About Preemptive and Reactive Genetic Testing by Race-Ethnicity and Rurality, n=1600

	Race/Ethnicity n (%)					**Rurality n (%)**			
Choices	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**	**Total**
Preemptive	76 (13.9%)	34 (8.3%)	23 (9.9%)	57 (13.8%)	**P < 0.0001**	49 (9.4%)	141 (13.1%)	**P < 0.0001**	190 (11.9%)
Reactive	23 (4.2%)	21 (5.1%)	13 (5.6%)	56 (13.6%)		17 (3.3%)	96 (8.9%)		113 (7.1%)
Both	149 (27.3%)	81 (19.7%)	62 (26.7%)	92 (22.3%)		113 (21.7%)	271 (25.1%)		384 (24.0%)
None	297 (54.5%)	275 (66.9%)	134 (57.8%)	207 (50.2%)		341 (65.6%)	572 (53.0%)		913 (57.1%)
Total	545 (34.1%)	411 (25.7%)	232 (14.5%)	412 (25.8%)		520 (32.5%)	1080 (67.5%)		1600

4.3.4. Preferences of Genetic Testing

4.3.4.1. Comfort with different sampling methods

When asked how comfortable respondents were with three different ways of genetic testing, respondents were significantly more comfortable with buccal swab (87%) and saliva (89%) as a genetic testing sample compared to blood draw (71%). With regards to blood draw, results varied significantly (P = 0.001) for this question when stratified by race (Table 5). For example, only 65% Asians and 67% Hispanics were comfortable using blood as a sampling choice compared to 77% Whites.



*** Very comfortable and comfortable were merged as "Comfortable" while very uncomfortable and uncomfortable responses were merged as "Uncomfortable".

Figure 18: Comfort With Different Sampling Methods, n=1600

Table 23: Comfort With Different Sampling Methods by Race-Ethnicity and Rurality, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Sampling choice	**Level of comfort**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Blood	**Comfortable**	421 (77.3%)	285 (69.3%)	150 (64.7%)	277 (67.2%)	**P = 0.001**	360 (69.2%)	773 (71.6%)	P = 0.13
	Neither comfortable nor uncomfortable	60 (11.0%)	49 (11.9%)	41 (17.7%)	60 (14.6%)		63 (12.1%)	147 (13.6%)	
	Uncomfortable	64 (11.7%)	77 (18.7%)	41 (17.7%)	75 (18.2%)		97 (18.7%)	160 (14.8%)	
Buccal Swab	**Comfortable**	481 (88.3%)	356 (86.6%)	204 (87.9%)	356 (86.4%)	P = 0.91	457 (87.9%)	940 (87.0%)	P = 0.12
	Neither comfortable nor uncomfortable	38 (7.0%)	35 (8.5%)	15 (6.5%)	36 (8.7%)		32 (6.1%)	92 (8.5%)	
	Uncomfortable	26 (4.8%)	20 (4.9%)	13 (5.6%)	20 (4.9%)		31 (6.0%)	48 (4.4%)	
Saliva	**Comfortable**	498 (91.4%)	354 (86.1%)	206 (88.8%)	365 (88.6%)	P = 0.26	457 (87.9%)	966 (89.4%)	P = 0.055
	Neither comfortable nor uncomfortable	27 (5.0%)	29 (7.1%)	16 (6.9%)	26 (6.3%)		28 (5.4%)	70 (6.5%)	
	Uncomfortable	20 (3.7%)	28 (6.8%)	10 (4.3%)	21 (5.1%)		35 (6.7%)	44 (4.1%)	

*** Very comfortable and comfortable were merged as “Comfortable” while very uncomfortable and uncomfortable responses were merged as “Uncomfortable”.

4.3.4.2. Preference regarding the choice of sampling method

Forty percent of the total respondents selected buccal swab as their preferred method of genetic testing sample while similar percentages of respondents chose blood draw (31%) and saliva (29%). No significant differences were observed when stratified by race-ethnicity and rurality (Table 6).

Table 24: Choice of Sampling Methods by Race-Ethnicity and Rurality, n=1600

	Race/Ethnicity n (%)					**Rurality n (%)**			
Choices	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**	**Total**
Blood	174 (31.9%)	137 (33.3%)	61 (26.3%)	131 (31.8%)	**P = 0.050**	175 (33.7%)	328 (30.4%)	P = 0.19	503 (31.4%)
Buccal Swab	211 (38.7%)	171 (41.6%)	85 (36.6%)	173 (42.0%)		211 (40.6%)	429 (39.7%)		640 (40.0%)
Saliva	160 (29.4%)	103 (25.1%)	86 (37.1%)	108 (26.2%)		134 (25.8%)	323 (29.9%)		457 (28.6%)
Total	545 (34.1%)	411 (25.7%)	232 (14.5%)	412 (25.8%)		520 (32.5%)	1080 (67.5%)		1600

4.3.4.3. Preferences in sharing genetic test results

Significantly more respondents were comfortable with sharing their test results to healthcare professionals compared to employers and health insurance providers (Figure 6). For instance, 90% of the respondents were somewhat to very comfortable sharing their results with doctor compared to only 19% wanted to share results with their employer. A greater proportion of respondents were very comfortable or somewhat comfortable sharing their results with their family and friends (62%) compared to pharmacists (51%). When stratified by rurality, racial and ethnic groups, results varied significantly (Table 7). Significantly more urban respondents wanted to share their results with employers compared to rural people (20.9% vs. 14.6%, P = 0.01). Only 13% Black and 15% Asian were comfortable sharing their genetic testing results with their employers compared to 21% White and 25% Hispanic population (P = 0.001). Besides, Asians were significantly less comfortable to share their genetic testing results with pharmacists compared to the other counterparts (Asian 45% vs. Black 53% vs. White 55% vs, Hispanic 58%, P = 0.01).

When stratified by rurality, statistically significant differences were observed as well (Table 7). For example, almost double rural respondents were not willing to share their genetic testing results with doctors compared to urban respondents (6% vs. 3%, P = 0.005). Percentages of respondents being uncomfortable were increased when asked about sharing results with pharmacists (rural 27.3% vs. urban 22.2%, P = 0.03). Similar to that, higher percentages of rural respondents were uncomfortable sharing their results with employers compared to urban respondents (63.1% vs. 56.1%, P = 0.01). Significantly (P = 0.04) less than half of the rural respondents were willing to share their results with genetic testing companies compared to 56% urban residents.

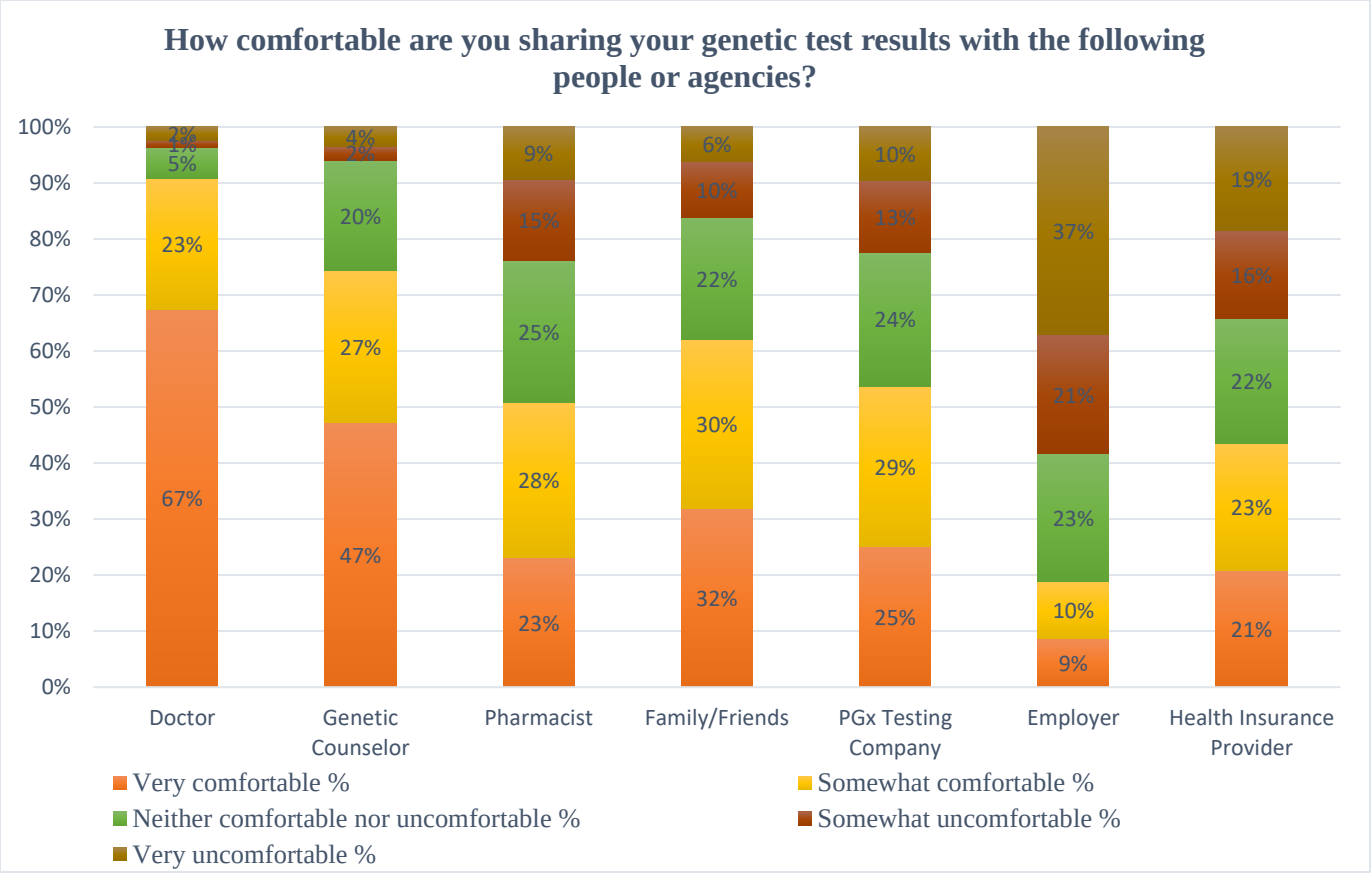


Figure 19: Comfort Around Sharing Genetic Test Results With Different People or Organizations, n=1600

Table 25: Comfort Around Sharing Genetic Test Results With Different People or Organizations, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Individual receiving results	**Level of comfort**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Doctor	**Comfortable**	507 (93.0%)	366 (89.1%)	205 (88.4%)	375 (91.0%)	P = 0.13	459 (88.3%)	994 (92.0%)	**P = 0.005**
	Neither comfortable nor uncomfortable	20 (3.7%)	24 (5.8%)	19 (8.2%)	24 (5.8%)		30 (5.8%)	57 (5.3%)	
	Uncomfortable	18 (3.3%)	21 (5.1%)	8 (3.5%)	13 (3.16%)		31 (6.0%)	29 (2.7%)	
Pharmacist	**Comfortable**	303 (55.6%)	186 (45.3%)	114 (49.1%)	211 (51.2%)	P = 0.06	241 (46.4%)	573 (53.1%)	**P = 0.03**
	Neither comfortable nor uncomfortable	121 (22.2%)	110 (26.8%)	65 (28.0%)	108 (26.2%)		137 (26.4%)	267 (24.7%)	
	Uncomfortable	121 (22.2%)	115 (28.0%)	53 (22.8%)	93 (22.6%)		142 (27.3%)	240 (22.2%)	
Genetic Counselor	**Comfortable**	411 (75.4%)	299 (72.8%)	170 (73.3%)	309 (75.0%)	P = 0.26	377 (72.5%)	812 (75.2%)	P = 0.055
	Neither comfortable nor uncomfortable	102 (18.7%)	78 (19.0%)	52 (22.4%)	84 (20.4%)		97 (18.7%)	219 (20.3%)	
	Uncomfortable	32 (5.9%)	34 (8.3%)	10 (4.3%)	19 (4.6%)		46 (8.9%)	49 (4.5%)	

*** Very comfortable and comfortable were merged as “Comfortable” while very uncomfortable and uncomfortable responses were merged as “Uncomfortable”.

Table 25 (continued): Comfort Around Sharing Genetic Test Results With Different People or Organizations, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Test Results Willing to Share With	**Level of comfort**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Family or Friends	**Comfortable**	331 (60.7%)	254 (61.8%)	138 (59.5%)	269 (65.3%)	P = 0.13	315 (60.6%)	677 (62.7%)	P = 0.08
	Neither comfortable nor uncomfortable	123 (22.6%)	78 (19.0%)	61 (26.3%)	88 (21.4%)		106 (20.4%)	244 (22.6%)	
	Uncomfortable	91 (16.7%)	79 (19.2%)	33 (14.2%)	55 (13.4%)		99 (19.0%)	159 (14.7%)	
Genetic Testing Company	**Comfortable**	298 (54.7%)	218 (53.0%)	104 (44.8%)	240 (58.3%)	**P = 0.01**	256 (49.2%)	604 (55.9%)	**P = 0.04**
	Neither comfortable nor uncomfortable	119 (21.8%)	97 (23.6%)	77 (33.2%)	88 (21.4%)		138 (26.5%)	243 (22.5%)	
	Uncomfortable	128 (23.5%)	96 (23.4%)	51 (22.0%)	84 (20.4%)		126 (24.2%)	233 (21.6%)	
Employer	**Comfortable**	112 (20.76)	55 (13.4%)	34 (14.7%)	101 (24.5%)	**P < 0.001**	76 (14.6%)	226 (20.9%)	**P = 0.01**
	Neither comfortable nor uncomfortable	121 (22.2%)	89 (21.7%)	63 (27.2%)	91 (22.1%)		116 (22.3%)	248 (23.0%)	
	Uncomfortable	312 (57.3%)	267 (65.0%)	135 (58.2%)	220 (53.4%)		328 (63.1%)	606 56.1%)	

*** Very comfortable and comfortable were merged as “Comfortable” while very uncomfortable and uncomfortable responses were merged as “Uncomfortable”.

4.3.4.4. Preferences toward pharmacogenetic testing

When given the choice, the majority of the respondents (73.7%) chose preemptive testing over reactive testing (Figure 16). Compared to other racial and ethnic groups, statistically significantly more Black respondents chose reactive resting (Black 30.7% vs. Asian 2.58% vs. White 26.2% vs. Hispanic 20.9%, P = 0.013). Such significant differences were not observed when stratified by rurality (P = 0.14).

Table 26: Preferences Toward Pharmacogenetic Testing by Race-Ethnicity and Rurality, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Types of PGx testing	**Full Cohort**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Preemptive	1179 (73.7%)	402 (73.8%)	285 (69.3%)	166 (71.6%)	326 (79.1%)	**P = 0.013**	371 (71.4%)	808 (74.8%)	P = 0.14
Reactive	421 (26.3%)	143 (26.2%)	126 (30.7%)	66 (28.5%)	86 (20.9%)		149 (28.6%)	272 (25.2%)	
Total	1600	545 (34.1%)	411 (25.7%)	232 (14.5%)	412 (25.8%)		520 (32.5%)	1080 (67.5%)	

4.3.4.5. Preferences toward genetic testing in COVID-19 situation

When asked about whether they were afraid of leaving the house to get the genetic testing in-person, more than 80% of the respondents said that they were not afraid and only 16% said they were afraid (Figure 17). Responses to this question significantly varied by racial and ethnic groups, but not by rurality. Asians and Hispanics were most afraid of taking in-person genetic test compared to other racial and ethnic groups (Asian 24.1%, Hispanic 19.2%, White 12.5%, Black 12.9%, P < 0.0001).

Table 27: Preferences Toward Genetic Testing in COVID-19 Situation by Race-Ethnicity and Rurality, n=1600

		Race/Ethnicity n (%)					Rurality n (%)		
Whether they are afraid of leaving house to get test	**Full Cohort**	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic or Latino**	**Chi-square**	**Rural**	**Urban**	**Chi-square**
Afraid	256 (16.0%)	68 (12.5%)	53 (12.9%)	56 (24.1%)	79 (19.2%)	**P < 0.0001**	78 (15.0%)	178 (16.5%)	P = 0.19
Not Afraid	1298 (81.1%)	461 (84.6%)	338 (82.2%)	169 (72.8%)	330 (80.1%)		422 (81.2%)	876 (81.1%)	
Other	46 (2.9%)	16 (2.9%)	20 (4.9%)	7 (3.0%)	3 (0.7%)		20 (3.9%)	26 (2.4%)	
Total	1600	545 (34.1%)	411 (25.7%)	232 (14.5%)	412 (25.8%)		520 (32.5%)	1080 (67.5%)	

4.3.5. Perceptions Domain (Theory of Planned Behavior Questions)

A correlation graph is presented to understand how closely the items were related within each construct (Figure 7). Out of the eight diseases, only risk of Alzheimer's disease correlations are shown in Figure 7 since results were similar across different diseases. It was evident that attitude items highly correlate with each other and intention items highly correlate with each other. Although some correlation coefficients were small, perceived behavioral control (PBC) items were positively and significantly correlated with each other. Similarly, although some correlation coefficients were small, social norms items were positively and significantly correlated with each other. Of note, items 2 and 3 in the PBC construct were reverse coded for analysis. Also, two items (items 4 and 5) were removed from the PBC construct to improve internal consistency reliability, as described below in sections 5.1 and 5.2. This study found that items were factorable since the Bartlett's Test of Sphericity turned out significant ($P < 0.05$) and Kaiser-Meyer-Olkin measure of sampling adequacy (MSA) values were above 0.85 across all different diseases.

Alzheimer's Disease

Attitude

	Item_1	Item_2	Item_3	Item_4
Item_1	1.00			
Item_2	0.489 <.0001	1.00		
Item_3	0.474 <.0001	0.660 <.0001	1.00	
Item_4	0.419 <.0001	0.5810 <.0001	0.5890 <.0001	1.00

Perceived Behavioral Control

	Item_1	Item_2	Item_3
Item_1	1.00		
Item_2	0.096 0.0001	1.00	
Item_3	0.111 <.0001	0.523 <.0001	1.00

Social Norms

	Item_1	Item_2	Item_3
Item_1	1.00		
Item_2	0.147 <.0001	1.00	
Item_3	0.178 <.0001	0.509 <.0001	1.00

Intention

	Item_1	Item_2	Item_3
Item_1	1.00		
Item_2	0.687 <.0001	1.00	
Item_3	0.814 <.0001	0.727 <.0001	1.00

Figure 20: Pearson's Correlation Between Items in Each Construct For Alzheimer's Disease

4.3.5.1. Theory of Planned Behavior - Risk of Getting Certain Diseases

4.3.5.1.1. Mean scores

This section is considering Theory of Planned Behavior (TPB) in the context of intention to get a genetic test to predict risk of getting a certain disease. Descriptive statistics such as mean and standard deviation were provided for each of the constructs in table 10. For attitude, cancer had the highest mean scale score (4.14, SD 0.77) while Huntington's Disease had the lowest values (mean 3.79, SD 0.83). Similarly, the intention score indicated that the respondents had higher intention to get the genetic testing for cancer compared to other diseases in future. In bivariate analyses, mean scale scores for each construct were significantly different by race/ethnicity (all $P < 0.05$). For example, ANOVA with Tukey's post-hoc analysis showed that Hispanics had a significantly higher mean attitude scale score compared to Blacks and Asians when asked about cancer disease risk (Hispanics 4.25 vs. Blacks 4.08, $P<0.05$; Hispanics 4.25 vs. Asians 4.07, $P = 0.003$). Scores significantly varied by rurality as well for all constructs except cancer intention score ($P = 0.07$), macular degeneration attitude score ($P = 0.16$), and macular degeneration intention score ($P = 0.22$). For example, mean attitude scale score was significantly higher among urban residents compared to rural people for Alzheimer's disease, cancer, and Huntington's disease (all $P < 0.05$). However, perceived behavioral control was significantly higher for rural people compared to urban residents across all different diseases (all $P < 0.05$).

Table 28: Continuous Scale Scores For Each of the Constructs By Race-Ethnicity and Rurality For Risk of Diseases, n=1600

Diseases	Constructs	Overall (Mean ± SD)	Race-Ethnicity (Mean ± SD)						Rurality (Mean ± SD)		
			White	Black	Asian	Hispanic	ANOVA	Significant Comparisons	Rural	Urban	T-test
Alzheimer's Disease	Attitude	4.06 ± 0.77	4.00 ± 0.79	4.01 ± 0.81	4.00 ± 0.75	4.22 ± 0.69	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.99 ± 0.82	4.09 ± 0.74	**P = 0.02**
	PBC	3.69 ± 0.87	3.78 ± 0.86	3.72 ± 0.84	3.58 ± 0.83	3.59 ± 0.91	**P = 0.002**	W vs. H, W vs. A	3.77 ± 0.83	3.65 ± 0.88	**P = 0.01**
	Social Norms	2.83 ± 0.92	2.81 ± 0.91	2.52 ± 0.87	2.97 ± 0.80	3.08 ± 0.95	**P < 0.0001**	H vs. W, H vs. B, A vs. B	2.58 ± 0.86	2.95 ± 0.93	**P < 0.0001**
	Intention	3.76 ± 1.04	3.67 ± 1.11	3.69 ± 1.07	3.61 ± 1.03	4.05 ± 0.83	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.67 ± 1.11	3.81 ± 0.99	**P = 0.013**
Cancer	Attitude	4.14 ± 0.77	4.14 ± 0.77	4.08 ± 0.82	4.07 ± 0.75	4.25 ± 0.70	**P = 0.003**	H vs. B, H vs. A	4.07 ± 0.80	4.18 ± 0.75	**P = 0.01**
	PBC	3.74 ± 0.88	3.80 ± 0.89	3.85 ± 0.82	3.59 ± 0.81	3.62 ± 0.94	**P < 0.0001**	B vs. H, B vs. A, W vs. H, W vs. A	3.84 ± 0.83	3.69 ± 0.90	**P = 0.001**
	Social Norms	2.82 ± 0.94	2.78 ± 0.90	2.48 ± 0.92	2.99 ± 0.86	3.12 ± 0.95	**P < 0.0001**	H vs. W, H vs. B, A vs. W, A vs. B, W vs. B	2.56 ± 0.88	2.95 ± 0.95	**P < 0.0001**
	Intention	3.91 ± 0.99	3.88 ± 1.03	3.80 ± 1.08	3.81 ± 0.97	4.12 ± 0.80	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.84 ± 1.07	3.94 ± 0.95	P = 0.07
Huntington's Disease	Attitude	3.79 ± 0.87	3.72 ± 0.90	3.70 ± 0.92	3.75 ± 0.80	4.00 ± 0.80	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.68 ± 0.91	3.84 ± 0.85	**P = 0.001**
	PBC	3.72 ± 0.88	3.81 ± 0.89	3.80 ± 0.85	3.57 ± 0.80	3.63 ± 0.94	**P = 0.0002**	B vs. H, B vs. A, W vs. H, W vs. A	3.85 ± 0.84	3.66 ± 0.90	**P < 0.0001**
	Social Norms	2.81 ± 0.96	2.78 ± 0.95	2.44 ± 0.95	2.98 ± 0.83	3.12 ± 0.92	**P < 0.0001**	H vs. W, H vs. B, A vs. W, A vs. B, W vs. B	2.52 ± 0.90	2.95 ± 0.96	**P < 0.0001**
	Intention	3.55 ± 1.11	3.43 ± 1.18	3.42 ± 1.14	3.50 ± 1.05	3.86 ± 0.95	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.45 ± 1.15	3.59 ± 1.09	**P = 0.02**
Macular Degeneration	Attitude	3.94 ± 0.86	3.91 ± 0.89	3.89 ± 0.89	3.86 ± 0.83	4.06 ± 0.78	**P = 0.01**	H vs. W, H vs. B, H vs. A	3.89 ± 0.88	3.96 ± 0.85	P = 0.16
	PBC	3.75 ± 0.88	3.84 ± 0.88	3.79 ± 0.85	3.60 ± 0.81	3.66 ± 0.94	**P = 0.001**	B vs. A, W vs. H, W vs. A	3.86 ± 0.85	3.69 ± 0.89	**P = 0.0001**
	Social Norms	2.83 ± 0.96	2.77 ± 0.91	2.51 ± 0.95	3.04 ± 0.88	3.11 ± 0.99	**P < 0.0001**	H vs. W, H vs. B, A vs. W, A vs. B, W vs. B	2.58 ± 0.92	2.95 ± 0.96	**P < 0.0001**
	Intention	3.74 ± 1.04	3.70 ± 1.07	3.70 ± 1.09	3.62 ± 1.01	3.92 ± 0.93	**P = 0.001**	H vs. W, H vs. B, H vs. A	3.70 ± 1.10	3.77 ± 1.01	P = 0.22

4.3.5.1.2. Internal consistency

Table 11 shows the internal consistency i.e., Cronbach's alpha coefficients of the four constructs across four different diseases. The Cronbach's alpha was consistent and above 0.7 threshold for both attitude and intention constructs. For the other two constructs, PBC and subjective norms, the observed values for these two constructs were moderate. Of note, items 4 and 5 of the PBC construct were removed from the PBC scale in order to improve the Cronbach's alpha statistics for that construct. Prior to removing items 4 and 5, Cronbach's alpha ranged from 0.16 to 0.26 for the PBC construct in this section.

Table 29: Reliability Assessment Scores for Measures Related to Risk of Disease

Themes of Questionnaire	Number of Items	IC for Alzheimer's	IC for Cancer	IC for Huntington's Disease	IC for Macular Degeneration
Attitude	4	0.82	0.84	0.82	0.84
Perceived behavioral control	3	0.53	0.58	0.59	0.59
Subjective norms	3	0.55	0.57	0.59	0.61
Intention	3	0.90	0.90	0.92	0.91

IC = Internal Consistency, Cronbach's Alpha

4.3.5.1.3. Association between Intention and Other Predictors for Risk of Disease

Intention was dichotomized where higher intention was defined as greater than or equal to median score and less than median scores mean lower intention. Although dichotomization is not usually preferred, there are certain cases where this procedure can be justified.[174,175] The distribution of our dependent variable is mostly right skewed and provided us the opportunity to dichotomize. In addition, the cut-off point i.e., median split was decided earlier. Hence, it was not data-driven as recommended by Naggara et al.[231] Based on the logistic regression model below, attitude was a very strong predictor for intention across all the diseases. Notably, each additional increase of one unit in PBC score was associated with a decrease in the odds of genetic testing intention for Alzheimer's disease (OR 0.81, 95% CI 0.69 to 0.95) and macular degeneration (OR 0.80, 95% CI 0.67 to 0.95). Although such inverse relationship was observed, it was not statistically significant for other two diseases. In contrast, as the social norms score increases, the odds of intention became higher for all the four diseases (OR 1.26, 95% CI 1.07 to 1.48 for Alzheimer's disease, OR 1.46, 95% CI 1.21 to 1.76 for cancer disease, OR 1.40, 95% CI 1.17 to 1.69 for Huntington's disease, and OR 1.42, 95% CI 1.18 to 1.71 for macular degeneration). Compared to urban people, rural residents had higher odds of intention for all diseases except Alzheimer's disease (OR 1.49, 95% CI 1.09 to 2.04 for cancer disease, OR 1.62, 95% CI 1.17 to 2.24 for Huntington's disease, and OR 1.44, 95% CI 1.05 to 1.99 for macular degeneration). Smoking was a significant predictor for Alzheimer's disease and Huntington's disease (OR 1.48, 95% CI 1.11 to 1.98 for Alzheimer's disease, and OR 1.42, 95% CI 1.03 to 1.95 for Huntington's disease). Race was not a significant predictor of intention to get a genetic test for risk of disease.

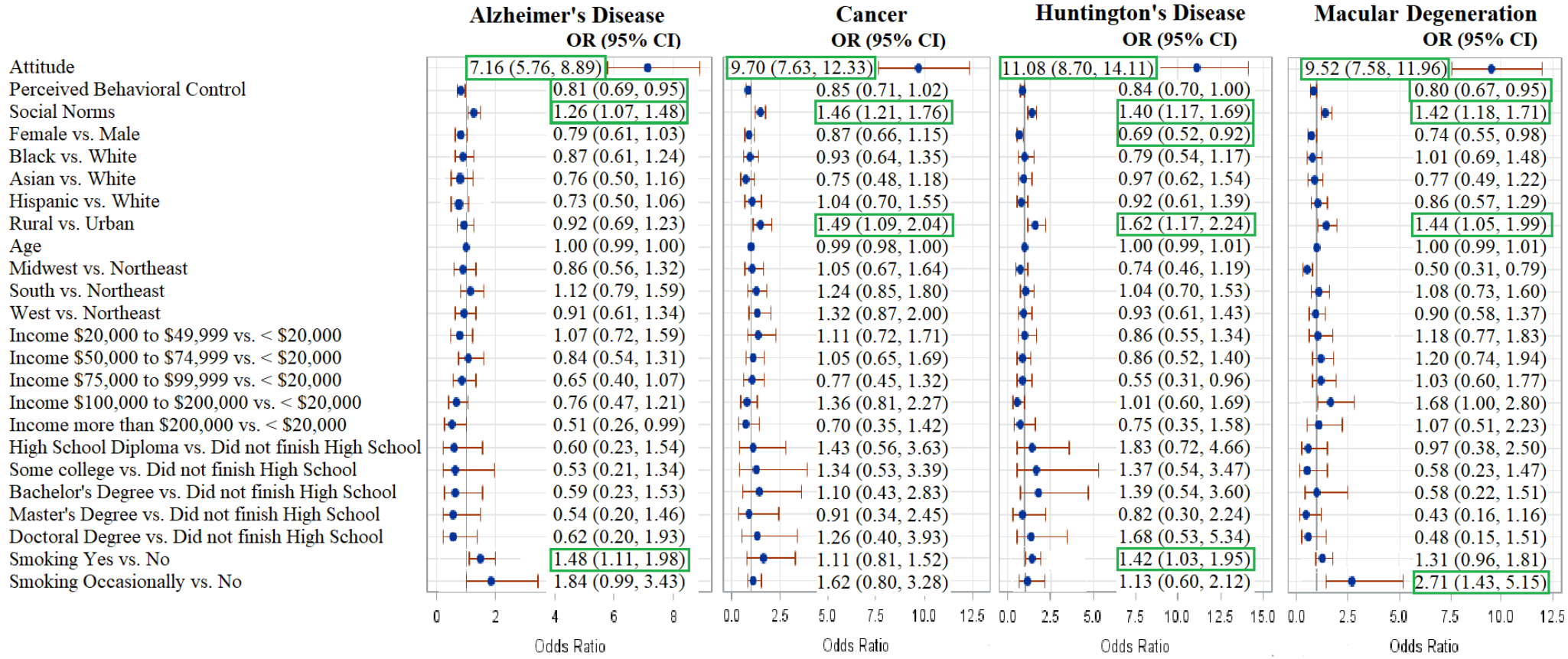


Figure 21: Logistic Regression Model for Risk of Disease Section

*Outcome variable=Intention dichotomized on median scale score for each disease (<median=low intention; ≥median=high intention).

4.3.5.2. Theory of Planned Behavior – Choice of Treatments for Certain Diseases

4.3.5.2.1. Mean Scores

Departing from the section above, this section is considering Theory of Planned Behavior (TPB) in the context of intention to get a genetic test to help guide choice of treatment for a certain disease. Table 12 summarizes the distribution of means, medians, and ranges for each of the constructs. Similar to the risk of disease section, cancer had the highest attitude and intention mean scale scores (mean 4.06, SD 0.80 and mean 4.20, SD 0.85) followed by heart disease (mean 4.06, SD 0.85 and mean 4.04, SD 0.89) while depression had the lowest values (mean 3.72, SD 1.01 and mean 3.83, SD 0.99). In bivariate analyses, scores significantly varied by race and ethnicity for all constructs except cancer intention score (all $P < 0.05$). When stratified by rurality, scores were significantly different for the majority of constructs, but not for all. With regards to cancer and depression, mean attitude scale score was significantly higher for urban residents compared to rural people ($P = 0.01$). However, mean PBC and social norms scores were significantly higher among rural residents compared to urban people across all different diseases (all $P < 0.05$). None of the intention scores were significantly different between the rural and urban residents.

Table 30: Continuous Scale Scores For Each of the Constructs By Race-Ethnicity and Rurality For Choice of Treatments, n=1600

		Overall (Mean ± SD)	Race-Ethnicity (Mean ± SD)						Rurality (Mean ± SD)		
Diseases	**Constructs**		**White**	**Black**	**Asian**	**Hispanic**	**ANOVA**	**Significant Comparisons**	**Rural**	**Urban**	**T-test**
Cancer	Attitude	4.06 ± 0.80	4.06 ± 0.79	3.99 ± 0.82	3.98 ± 0.81	4.19 ± 0.77	**P = 0.001**	H vs. B, H vs. A	3.98 ± 0.84	4.10 ± 0.77	**P = 0.01**
	PBC	3.66 ± 0.86	3.76 ± 0.86	3.71 ± 0.83	3.47 ± 0.78	3.58 ± 0.93	**P < 0.0001**	W vs. H, W vs. A, B vs. A	3.77 ± 0.82	3.60 ± 0.88	**P = 0.0002**
	Social Norms	2.90 ± 0.96	2.85 ± 0.90	2.57 ± 0.94	3.07 ± 0.86	3.21 ± 1.01	**P < 0.0001**	H vs. W, H vs. B, A vs. W, A vs. B, W vs. B	2.60 ± 0.88	3.05 ± 0.97	**P < 0.0001**
	Intention	4.20 ± 0.85	4.22 ± 0.87	4.20 ± 0.88	4.07 ± 0.85	4.25 ± 0.80	P = 0.07	None	4.20 ± 0.87	4.20 ± 0.85	P = 0.99
Chronic Pain	Attitude	3.73 ± 0.96	3.63 ± 1.00	3.71 ± 0.95	3.63 ± 0.93	3.92 ± 0.91	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.66 ± 1.00	3.76 ± 0.94	P = 0.06
	PBC	3.70 ± 0.86	3.82 ± 0.85	3.78 ± 0.82	3.51 ± 0.78	3.59 ± 0.93	**P < 0.0001**	B vs. H, B vs. A, W vs. H, W vs. A	3.82 ± 0.82	3.65 ± 0.88	**P = 0.0002**
	Social Norms	2.81 ± 0.99	2.73 ± 0.96	2.48 ± 0.95	2.99 ± 0.89	3.13 ± 1.00	**P < 0.0001**	H vs. W, H vs. B, A vs. W, A vs. B, W vs. B	2.54 ± 0.93	2.94 ± 0.99	**P < 0.0001**
	Intention	3.92 ± 0.94	3.88 ± 0.95	3.91 ± 0.95	3.80 ± 0.97	4.07 ± 0.90	**P = 0.002**	H vs. W, H vs. A	3.92 ± 0.96	3.92 ± 0.94	P = 0.87
Depression	Attitude	3.72 ± 1.01	3.65 ± 1.02	3.59 ± 1.04	3.63 ± 0.96	3.99 ± 0.94	**P < 0.0001**	H vs. W, H vs. B, H vs. A	3.63 ± 1.04	3.77 ± 0.99	**P = 0.01**
	PBC	3.69 ± 0.87	3.78 ± 0.87	3.76 ± 0.82	3.52 ± 0.78	3.60 ± 0.95	**P < 0.0001**	B vs. H, B vs. A, W vs. H, W vs. A	3.82 ± 0.81	3.62 ± 0.90	**P < 0.0001**
	Social Norms	2.86 ± 1.01	2.77 ± 0.98	2.52 ± 0.96	3.06 ± 0.91	3.19 ± 1.02	**P < 0.0001**	H vs. W, H vs. B, A vs. W, A vs. B, W vs. B	2.57 ± 0.95	3.00 ± 1.01	**P < 0.0001**
	Intention	3.83 ± 0.99	3.79 ± 0.97	3.77 ± 1.05	3.77 ± 0.98	3.99 ± 0.96	**P = 0.003**	H vs. W, H vs. B, H vs. A	3.80 ± 1.03	3.85 ± 0.98	P = 0.19
Heart Disease	Attitude	4.06 ± 0.85	4.04 ± 0.85	4.05 ± 0.87	3.94 ± 0.85	4.17 ± 0.81	**P = 0.01**	H vs. A	4.03 ± 0.91	4.08 ± 0.82	P = 0.27
	PBC	3.63 ± 0.87	3.74 ± 0.87	3.71 ± 0.81	3.45 ± 0.79	3.51 ± 0.95	**P < 0.0001**	B vs. H, B vs. A, W vs. H, W vs. A	3.73 ± 0.82	3.58 ± 0.89	**P = 0.001**
	Social Norms	2.92 ± 0.98	2.82 ± 0.96	2.62 ± 0.98	3.03 ± 0.87	3.27 ± 0.97	**P < 0.0001**	H vs. W, H vs. B, H vs. A, A vs. W, A vs. B, W vs. B	2.64 ± 0.97	3.05 ± 0.96	**P < 0.0001**
	Intention	4.05 ± 0.89	4.01 ± 0.90	4.03 ± 0.92	3.91 ± 0.94	4.18 ± 0.81	**P = 0.002**	H vs. W, H vs. A	4.01 ± 0.92	4.06 ± 0.88	P = 0.33

4.3.5.2.2. Internal Consistency

Table 13 shows the internal consistency i.e., Cronbach's alpha coefficients of the four constructs across four different diseases. Similar findings to the risk of disease section were observed here with attitude and intention having high internal consistency (range, 0.83 to 0.90). Of note, items 4 and 5 of the PBC construct were removed from the PBC scale in order to improve the Cronbach's alpha statistics for that construct. Prior to removing items 4 and 5, Cronbach's alpha ranged from 0.23 to 0.27 for the PBC construct in this section.

Table 31: Reliability Assessment Scores for Measures Related to Choice of Treatment Section

Themes of Questionnaire	Number of Items	IC for Cancer	IC for Chronic Pain	IC for Depression	IC for Heart Disease
Attitude	4	0.83	0.86	0.87	0.85
Perceived behavioral control	3	0.54	0.55	0.55	0.54
Subjective norms	3	0.58	0.62	0.61	0.60
Intention	3	0.89	0.89	0.90	0.89

IC = Internal Consistency, Cronbach's Alpha

4.3.5.2.3. Association between Intention and Other Predictors for Choice of Treatments Section

Similar to the risk of diseases section, attitude was a very strong predictor for intention (dichotomized on median values as higher intention vs. lower intention) across all the diseases for this choice of treatments section. In contrast to the risk of diseases section, each additional increase of one unit in PBC score was associated with an increase in the odds of genetic testing intention. However, it was statistically significant for chronic pain only (OR 1.28, 95% CI 1.07 to 1.52). Besides, with a unit increase in social norm score, the odds of intention increases for depression (OR 1.28, 95% CI 1.08 to 1.52). Compared to people residing in urban areas, rural residents had higher odds of intention to get testing to help with chronic pain (OR 1.43, 95% CI 1.05 to 1.94). Although respondents who smoke had higher intention for genetic testing compared to those who did not, smoking was not a statistically significant predictor for any of the diseases. Race was not a significant predictor of intention to get genetic testing to guide choice of treatment.

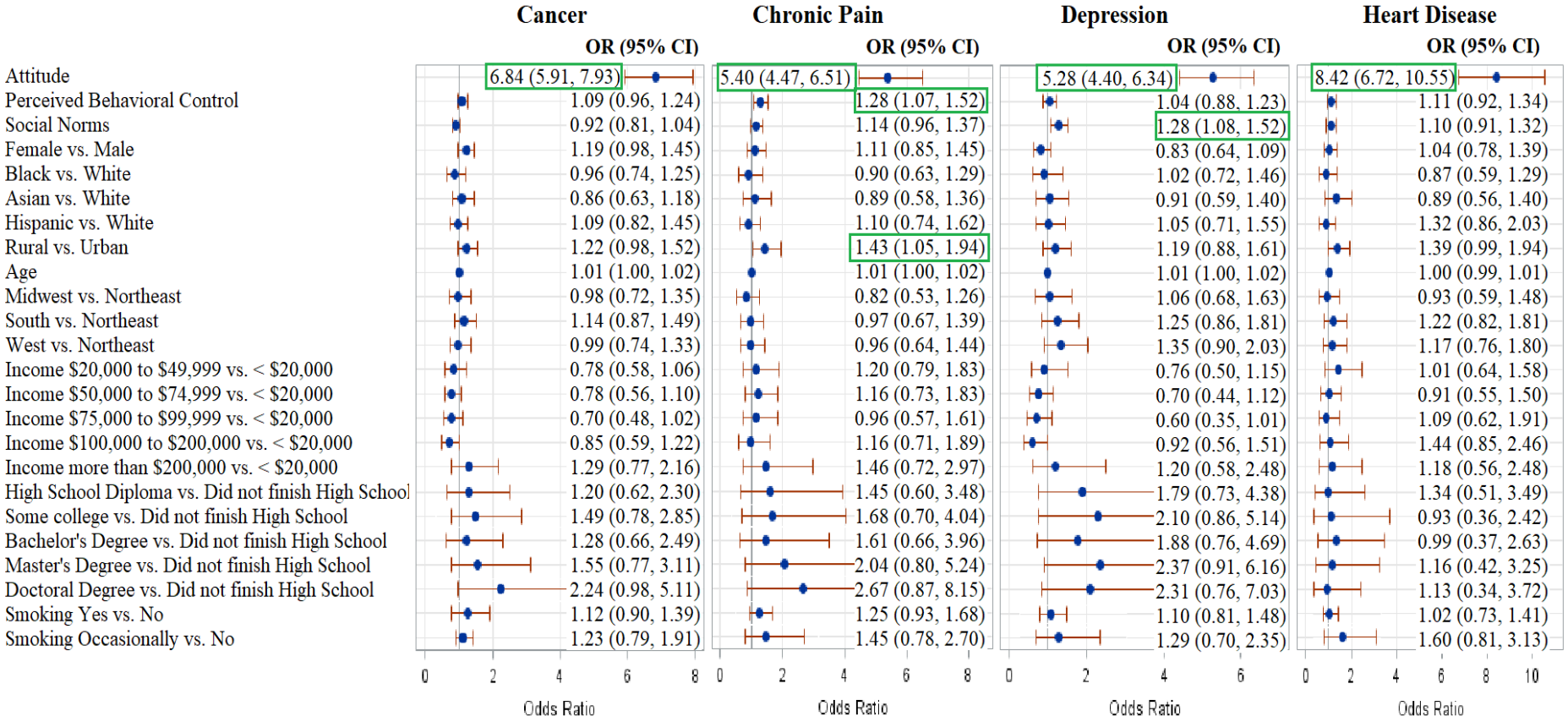


Figure 22: Logistic Regression Model for Choice of Treatments Section

*Outcome variable=Intention dichotomized on median scale score for each disease (<median=low intention; ≥median=high intention).

Chapter Five

Discussion

This study assessed three different aspects of genetic testing: 1) access, 2) implementation experience, and 3) awareness, preferences, and perceptions. In the first aim, we examined the geographic access to genetic testing clinics for people living in the US. For aim 2, we synthesized the current evidence on the barriers and facilitators to genetic testing implementation in a healthcare setting. Finally, a Qualtrics survey was conducted in aim 3 to assess the awareness, preferences, and perceptions toward genetic testing among the US general public. All three aims were successfully completed.

5.1. Aim 1 Summary and Implications

As to our knowledge, this is the first study to characterize population-based geographic access to genetic testing centers while examining for racial disparities as well. The easier access to online direct-to-consumer (DTC) genetic testing and telehealth options may pose questions on the importance of having conventional genetic testing physical locations. Although literature shows that DTC testing is getting popular and increasing awareness among people, the ACMG guideline strongly supports the conventional genetic testing procedure performed in an appropriate laboratory and inspected by an appropriate agency.[58] This aim was completed because literature indicated that population who live longer distance from the healthcare facilities had a negative impact on their health outcomes.[8,232] Findings from our road network analysis revealed that about more than 3 million people in the United States, around 1% of the total population, had to drive 180 minutes and more to the nearest genetic testing center. These

findings reported here are generally consistent with access issue to other types of healthcare services. For example, in 2007, Onega et al., reported that approximately 0.3% of total US population, based on the US Census 2000, lived outside of 180-minutes driving time to the nearest specialized cancer care defined as any oncologist regardless of their institutional affiliation.[80] The percentage goes up to 5.2% when analyzed for academic-based cancer care and 23.5% for National Cancer Institute (NCI) based cancer care.[80] Delamater et al., reported that around 6% of the total US population were living outside of 180-minutes driving time to hematopoietic cell transplantation (HCT) services.[233] In 2015, it was revealed that around 2% of the total US population had to drive more than an hour to go to a hospital with surgical capabilities.[234] Similarly, another recent article highlighted that a significant percentage of the US population had to drive more than an hour to go to a nearest lung cancer screening center.[235] These studies suggest a portion of the US total population had always been experiencing travel burden regardless of the types of treatment facilities. Even emergency medical service units took 26 minutes on average from the time of a 911 call to arrive on the scene in rural areas.[236]

Maldistribution of healthcare workforce and facilities had always been a major issue in terms of access to care in the US and our findings confirmed that access to genetic testing facilities is also problematic. Therefore, it is important to assess how well dispersed healthcare facilities are across the United States. Our study included 1,284 genetic testing clinics. Onega et al., had 58 NCI cancer centers, 280 academic-based care, and 8,701 any specialized cancer care.[80] A total of 229 HCT facilities were involved in the Delamater study while 698 lung cancer screening centers were incorporated in the Niranjan et al., study.[233,235] Similar to our analysis, Diaz et al., had 1,284 hospitals with surgical care.[234] Although 1,284 clinics may seem like an adequate number, they are not well distributed throughout the U.S. For example, more than a

third of the facilities were located in New York Mid Atlantic region. Similar clustering was observed in other studies as well. For example, NCI cancer centers were mostly located in the Eastern part of the country while a large number of lung cancer screening centers were seen in the Northeastern part of the US.[235,237] According to the Pew Research Center, people living in the Kansas, Iowa, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota states had to travel longer to a hospital than those living in the East coast.[88] This trend was also observed in our study. Compared to the Eastern zones, where facilities are clustered (New York Mid Atlantic and New England regional networks), Kansas and North Dakota had higher percentages of their population driving much longer to go to the nearest genetic testing clinics. In these areas where a longer travel time is required, it is critical to determine if the travel burden translates into a delay in obtaining a genetic testing. Factors that could affect the delay in these areas could include: ability to drive, whether they own a vehicle, having a caregiver who can provide a ride, etc.

In addition, our study found that different racial groups lived in different driving categories across the US. Specifically, 58% of Whites had to drive less than 30 mins to the nearest center, when significantly higher percentages of Blacks and Asians had similar distance to travel. The term "reversed racial disadvantage" was first introduced in an article that examined the disparities in geographical accessibility of NCI cancer centers in the US.[237] Authors of that study revealed that non-Hispanic Whites had significantly lower geographic accessibility compared to non-Hispanic Blacks and Asians.[237] Consistent to this, Whites had the worst geographic access to HCT service compared to the minority populations.[233] Another study also supported this notion reporting non-Hispanic Whites had to travel more to go to the nearest routine care or urgent care compared to non-Hispanic others.[238] One possible reason for this could be because geographic access to the nearest testing facility is limited in rural areas and the

population residing in rural US is predominantly non-Hispanic White.[239] This hints that although there are supports from existing literature, the observed difference could be because of rural-urban issues rather than a reversed racial disadvantage. Census tract level data on rurality was not available when this study was performed. Therefore, when data becomes available, it is essential to examine geographic access by rurality to identify if rurality is an important factor affecting limited access.

COVID-19 pandemic may have taught us to bring innovative solutions in our healthcare to ensure better outcomes. The University of Texas Southwestern Cancer Genetics Program adapted their testing methods because of COVID-19 pandemic where most patients got the testing kits via mail from the laboratory and even mobile phlebotomy was arranged in some cases.[240] Randell et al., reported that home saliva kits yielded highest return rates while mobile phlebotomy was successful as well.[241] One could be skeptical about quantity and quality of saliva obtained by the patients themselves because they may not be an expert in sample collection but all specimens did provide sufficient material for genetic analysis. Similar steps can be taken by the genetic testing clinics to reduce travel burden for testing purpose across the US. When patient can't come to the service, the service should be made available to the patients.

When the analysis looked at specific regional genetics network and individual states, results varied significantly, specifically for both less than 30 minutes driving distance and outside of 180 minutes driving zone. A number of states in the mainland of US including Colorado, Maryland, New Jersey, New York, Rhode Island had almost 90% of their population living within 30 minutes driving distance. But results varied significantly when stratified by race even for these states. For example, compared to around 90% Blacks and Asians, less than 70% Whites lived inside 30 minutes driving zone in Colorado. This suggests findings from this study

can be useful despite the fact that majority of the population of these states are living nearby to the genetic testing clinics. Overall, several interventions can help address limited access. First, community pharmacies should be incentivized to implement genetic testing services. Second, healthcare facilities should provide an option for mailing in testing samples for genetic tests. Lastly, more testing facilities need to be added in some of the states where significant number of population have limited access.

5.2. Aim 2 Summary and Implications

Barriers and facilitators to implement genetic testing were described using the five domains of CFIR i.e., intervention characteristics, inner settings, outer settings, characteristics of the individuals, and process in our scoping review. Previous studies recommended to continuously monitor the barriers and facilitators to avoid unprecedented issues throughout the implementation process.[242] Identifying barriers and facilitators while organizing them based on the major CFIR domains in a systematic review has been a captivating strategy to aid future implementations across different healthcare interventions.[147,243,244] Since the objective was to identify key factors instead of qualitative evidence synthesis, scoping review seemed more befitting than the typical systematic review. One striking finding from this scoping review is that majority of the barriers and solutions in this scoping review were surrounded intervention characteristics and inner settings. While an adequate number of factors were described in the outer settings, most included studies in our scoping review did not mention barriers and facilitators related to the characteristics of individuals and process domains. Literatures suggest that this should not be unexpected. A systematic review of the use of the CFIR showed that the intervention characteristics, inner settings, and characteristics of individuals were cited in large number of studies compared to the other two domains of CFIR.[245] Besides, it is also true that the total number of constructs is higher for intervention characteristics and inner settings compared to the other three domains. In another recent systematic review on the barriers and facilitators of the implementation of alcohol screening and brief intervention among primary care health professionals, process was the least described section based on the available studies.[246] There is less guidance on which domains should be preferred for genetic testing implementations. The IGNITE network common measures working group (CMG) highlighted 10 high-priority CFIR

constructs for implementation of genomic medicine interventions in clinical care that belongs to all major domains except the outer setting.[125] In our study, we placed all the patient characteristics as outer settings. But the IGNITE study did label the patient characteristics as high-priority and grouped them as non-CFIR domain.[125] Therefore, with regards to genetic testing implementation, all the five major domains of CFIR should be considered and incorporated in the planning of genetic testing service implementation.

Factors relating to cost and reimbursement were described as a major barrier in the intervention characteristics. Although the cost of single gene test declined over time, previous studies found that multigene panel was used for the same claim instead of single gene testing and it was more costly.[94] One of the studies in our scoping review did suggest using single gene testing instead of multigene panel to save money (128).[183] A large systematic review identified that most multigene panels are not covered by payers in the US and no uniformity was observed regarding how test coverage is assessed.[247] Most often multigene panels do not fit the standard definition of "medical necessity" required for the coverage.[247] However, multigene panels could be cost effective in the long run.[248-250] This creates a dilemma to choose between the two types of genetic testing. Lynce et al., did provide some suggestions regarding the confusion while stating that single gene testing could be favored over multigene if the patient's personal and family histories are strongly indicative of a particular disease.[251] Besides, systematic registries of payer coverage policies for multigene testing are required to fully characterize the multigene panels and should be updated based on the available evidence on utilities frequently.[247] Another possible reason for this barrier could be large numbers of misordered tests which ultimately adds unnecessary costs. For example, a recent study reviewed charts associated with genetic testing billing codes for common genetic tests and found that more than a third of the tests were

misordered based on the published clinical practice guidelines.[252] Over a three months period, this specific institution could have saved $20,000 if they followed the clinical practice guidelines appropriately.[252] Hence, both genetic counselor's support and additional education programs for healthcare providers to keep them updated with new recommendations from corresponding clinical societies are required to comply with the best clinical practices which will eventually save money.[252] Because guidelines are based on the evidence, another major barrier identified in our scoping review is the lack of utility studies to provide evidence for genetic testing uptake. This barrier also limits the payer to determine coverage policies.[253-258] It is essential to recruit large and diverse study population for clinical outcomes and simultaneously provide focus on implementation research to address this barrier in the future.[259]

Technical issues such as integrating genetic information to EHR plays a key role in genetic testing implementation. Previous studies discussed this challenge and provided solutions. For example, Kho et al., recommended storing genetic test results externally to the EHR and then providing a link to follow through. Another similar solution is to create customized interface to connect the laboratory and the EHR which has already been established between FoundationOne and Vanderbilt University Medical Center.[260] Other solutions such as using scanned PDF files or images and storing them in discrete format were frequently mentioned in the existing literature and identified in our scoping review as well.[260-262] However, none of these solutions are without limitations. The American College of Medical Genetics and Genomics (ACMG) also published statements to help the providers, institutions, and vendors to identify best approaches to integrate genomic information into EHR.[263] Both national and international efforts are ongoing to address this barrier.[264]

Pharmacists are in a unique position to facilitate genetic testing implementation. This is because they are more accessible to patients compared to physicians or other qualified health care professionals. However, findings from this scoping review revealed that pharmacists are not considered as major healthcare providers of genetic tests.[265] This is consistent with the current literature. Although healthcare professionals do agree that pharmacists could play a vital role in implementing genetic testing, patients are still reluctant.[266] Patients were not even sure which provider should be in the frontline to provide PGx service and were not aware of pharmacists' expertise or training.[267] This lack of awareness about pharmacist's competency may help explain the trust issue, at least in part. To address the educational need, the American Association of Colleges of Pharmacy (AACP) Pharmacogenomics Special Interest Group recently updated the pharmacist competencies with 15 new competencies to advance pharmacy practice in pharmacogenomics.[268] In addition to patients and providers who may not recognize pharmacists to have a major role in genetic testing, in similar vein, laboratories may not allow pharmacists to order test or receive test results.[193] Findings from our scoping review discussed collaborative practice agreement to allow the pharmacists to order the pharmacogenetic tests.[193] To provide more clarification on pharmacist's task and ensure successful clinical implementation of pharmacogenomics, the American Society of Health-System Pharmacists (ASHP) published a recent statement on pharmacist's role in clinical pharmacogenomics and listed their responsibilities.[269] Doing so may help create trust among patients, providers and laboratories and can help facilitate the implementation of genetic testing.

The world of genetic testing is continuously thriving, and new information are being added every day. It is difficult for the stakeholders to keep up with the new knowledge over time.[270] This barrier was also discussed in our scoping review. For example, Liu et al., reported

that CPIC had published 24 different drug-gene interaction guidelines since the PREDICT program started in 2010.[220] In addition to a flexible structure that is suitable to changes and adjustments, different educational strategies including case-based discussions, long term education plans, and routine meetings were expected to address this barrier.[22,196,198,216,220] This scoping review also found that offering free genetic tests to both prescribers and pharmacists is an excellent strategy to gauge interest in genetic testing.[183,189,228] Not only it familiarizes the PGx-informed prescription to these stakeholders, but it also helps them to understand the impact of genetic testing on patients' lives.[228] However, it was unclear to what extent these free genetic tests should be offered. Although free tests can be offered in small research settings or pilot studies, cost would be a major barrier to offer it on a large scale. Indeed, it is well known that the implementation of pilot studies in a research setting may obtain success easily but does not guarantee favorable outcome when the interventions are implemented in real-world scenarios. Our findings suggest that long term program evaluations are required to verify the role of the discussed factors in the uptake of genetic testing across different healthcare settings using rigorous methods.

5.3. Aim 3 Summary and Implications

Except for the racial and ethnic categories, this survey successfully enrolled participants to match the expected quota prepared using the HINTS national survey. This is important because matching the survey cohort identical to a nationally representative sample improves generalizability of the study findings. In addition, a large sample of US adults was included in this survey including a substantial portion of racial and ethnic minorities as well as rural residents. Previous survey studies about genetic testing were lacking minority populations such as Black and Hispanics.[30,32] There are a few studies on rural population and their knowledge, perceptions, and attitude towards genetic testing. However, these studies were either state-based or city-based.[138,271-273] This current study included a large number of rural populations across the US which eventually helps in generalizability.

One of the striking findings from our survey is that respondents were aware of genetic testing and understood its role around risk of disease and inheritance, but half of the total respondents were not aware of genetic testing in the context of choice of treatments, identifying adverse events, and dosage correction. Blacks and rural residents were less knowledgeable about relationship between genetic testing and medications compared to their respective counterparts. This pattern is aligned with the published national survey results. Krakow et al., reported that although majority of the respondents heard about genetic tests regarding personal disease risk or inherited disease risk, only half of them were familiar with genetic test determining treatment or drug efficacy.[129] In contrast, one earlier study including national US sample reported higher interest in PGx testing but the questionnaire included general information about different uses of PGx testing as a part of education.[274] Therefore, the respondents had developed some basic knowledge before answering the question. A recent review of literature also found that most

patients were not aware of or knowledgeable about pharmacogenetic testing. This study findings also highlighted that more than half of the respondents never heard about specific pharmacogenetic testing such as preemptive and reactive testing.[275] To our knowledge, the current project is the first nationwide study to report general public awareness of these specific pharmacogenetic tests in the US.

Patient preference is important because it provides guidance for determining the best treatment and tailoring interventions to the patient's need.[276] The survey respondents were more likely to choose buccal swab and saliva over blood draw. This is understandable because non-invasive samplings methods are less fearful compared to blood draw. One of the major reasons why DTC testing is becoming more popular in the US is the use of non-invasive sample collection, saliva or swab.[277] When information regarding types of pharmacogenetic testing were presented, the majority of the respondents of this survey understood the benefits of preemptive testing and favored it over reactive testing if given the choice. However, it was noticed that non-Hispanic Blacks (31%) preferred reactive testing more than other counterparts (non-Hispanic White 26%, non-Hispanic Asian 29%, and Hispanic or Latino 21%). On a different note, it is possible that people with certain diseases may choose reactive over preemptive test and results may change depending on the existing disease conditions. Future studies should examine whether patients with diseases have different preferences toward these pharmacogenetic testing types compared to healthy people. Although previous studies discussed these two testing types from different perspectives, either in-general or from payers' perspective and cost-effectiveness aspect, no studies were found to report general public preference towards preemptive and reactive testing.[52,144,278,279] These findings could be an area for future educational interventions and additional research into the reasons behind these preferences. Besides, the survey

participants were careful about sharing their test results with different stakeholders. For example, participants preferred to share their test results with doctors and genetic counselors over pharmacists. But they were not comfortable sharing the results with employers and health insurance providers. The statistically significant differences between different racial and ethnic groups as well as the rural-urban populations for this survey question are noteworthy because future educational interventions can be tailored to target these specific subgroups based on the findings of this study. Since pharmacists are considered as "drug experts" and usually they are more accessible to the patients than any other healthcare providers, it is important to build a trusted relationship with patients to get access to the test results with the aim to improve their medication therapy. Our study also shows that a significant number of minorities, specifically the Asians and Hispanics, were afraid of in-person genetic testing after COVID-19 pandemic. There are reports about how Asians and Hispanics were most impacted by the pandemic which does explain the fear of going outside.[280,281]

Attitude and social norms were the two strongest predictors for intention to get tested for assessing the risk of diseases. However, when it comes to the choice of treatments, only attitude was consistently a significant predictor for genetic testing intention. One possible reason for this could be the observed difference in understanding genetic testing concepts. This current study found people living in the US are less aware of genetic testing in the context of choice of treatments compared to disease risk and heredity. Rimal et al., found that social norm had a weak relationship with intention when the behavior is unfamiliar.[282] This perfectly connects our findings regarding awareness and TPB constructs.

In particular, perceived behavioral control was negatively associated with intention to get genetic testing to learn about risk of diseases section, but positively impacted the intention when

genetic testing referred to the choice of treatments. There may be many possible explanations for these results. One potential explanation may be that differences in the PBC construct's association with intention might be due to differences in the number of respondents who had experience with each health condition, since conditions were different in each section (risk vs. treatment). Fewer respondents reported having/had conditions in the risk section compared to the treatment section (Alzheimer's: n=13, 0.81%; Huntington's: n=14, 0.88%; Macular Degeneration: n=53, 3.31%; compared to Chronic Pain: n=272, 17.00%; Depression: n=419, 26.19%; Heart Disease: n=100, 6.25%). Diseases presented in the risk section were also less commonly occurring conditions compared to those in the treatment section. All of this may mean that respondents were less familiar with conditions in the risk section compared to the treatment section, which may have influenced responses. However, opposite PBC-intention associations were still seen for cancer genetic testing (n=143; 8.94%) in the risk section compared to the treatment section. Another possible explanation may be that most diseases presented in the risk section had no cure and fewer treatment options compared to diseases presented in the treatment section (Alzheimer's Disease, Huntington's, and Macular Degeneration compared to Depression, Chronic Pain, and Heart Disease). Respondents with high PBC may have had less intention to get genetic testing for conditions with no cure or fewer/less well-known treatment options compared to conditions with more/well-known treatment options. For example, respondents with high PBC may feel that they don't want to know about their risk of having conditions with no cure/fewer treatment options, because this would create a situation in which they have less control over their health. On the other hand, respondents with higher PBC may feel that they already have resources and knowledge to help prevent the conditions mentioned in the risk section and see no added benefit of getting a genetic test. It is also possible that respondents

viewed genetic testing to inform their risk of disease in the future differently than genetic testing to inform their choice of treatment for diseases they were asked to imagine they already had in the present. This is supported by the behavioral economic principle of time preference, which includes two components: present-bias and discount rate.[283] Respondents with higher present-bias may have had more favorable intentions to undergo genetic testing to guide treatment choices for conditions they have in the present, and less favorable intentions to undergo genetic testing for risk of conditions they may acquire in the future. More research is needed to investigate how time preference affects intentions to get different types of genetic tests.

5.4. Limitations

There were several limitations in the first aim of this study. First, it is unknown whether the list obtained from the ACMG website is complete. It was a self-requested list and may not include some clinics that actually provide genetic services or collaborating with genetic testing centers. However, ACMG is a nationally recognized organization that represents the interests of different professional groups such as clinical genetics, genetic counselors, and laboratory genetics etc. and such comprehensive list cannot be retrieved from any other sources. However, it should be noted that, the list does not differentiate between different types of genetic tests. Second, facility characteristics such as number and types of genes tested, turnaround time, appointment time, and availability of genetic counselors are not available for most of the listed genetic testing centers. Although it limits the scope of analyses, the main objective of this study was not affected. Third, advanced road network analysis such as origin-destination (O-D) travel time matrix and 2-step virtual catchment area (2SVCA) methods to measure geographic access were not used in this analysis. This may have compromised the sensitivity of the calculated

distance to some extent but did not affect the overall study objective. Fourth, it should be noted that our study assessed driving time as a measure of geographic access. According to the Agency for Healthcare Research and Quality (AHRQ), the definition of access to care has four components including coverage, services, timeliness, and workforce.[63] Therefore, this study may have measured only one aspect of access to care, and as such we should interpret the results cautiously. Lastly, it is not possible to know whether people will use the closest genetic testing center. In certain circumstances, they may prefer to drive longer to visit a genetic testing center of their choice. Besides, with the rise of both COVID-19 pandemic and online genetic testing companies, people may not need to go to a genetic testing clinic.

A number of limitations did exist in the second aim as well. First, although we used PRISMA flow chart, it was not possible to report the findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 checklist because PRISMA primarily helps the authors to report a wide array of systematic reviews to assess the benefits and harms of a healthcare intervention. This study goal was not to synthesize evidence for pharmacogenetic testing, rather it focused on describing the real-world experiences of the implementation process and summarizes the barriers and facilitators from the literatures. Therefore, PRISMA was not the appropriate tool to report the findings of this study. Implementation science researchers typically use a few sets of theories/frameworks to guide the implementation process. The CFIR is one of the common frameworks in implementation science. The CFIR major domains was used as an alternate structure to report the study findings. Second, this study was not able to assess the risk of bias for each included study because examining systematic error in design and results were beyond the scope of the review method we chose. Along with the fact that risk of bias assessment is not necessary in scoping reviews, the absence

of risk of bias assessment will not restrain the significance of this study since the objective is to report the barriers and facilitators to pharmacogenetic implementation, not to evaluate the intervention effectiveness.[25] Third, this study did not use specific meta-synthesis approaches such as thematic analysis, meta-ethnography, and realist synthesis etc. to guide the qualitative meta-synthesis process. However, the goal was to descriptively list the barriers and facilitators and organize them using the CFIR framework. We believe our approach is valid for our objective and focus on implementation processes.

Similar to the previous two aims, limitations exist in the aim 3 of this study as well. First, Qualtrics recruits participants through online platforms. Therefore, the sample may not include US adults with low access to internet which could be labeled as sampling frame problem. Second, since Qualtrics was used to conduct the recruitment process, it was difficult to assess the response rates and non-response bias. However, pre-specified quotas were provided based on the HINTS survey to recruit a nationally representative sample of racial/ethnic minority participants with a range of different demographic characteristics to aid subgroup analysis. Third, some subgroups did not have adequate sample size. For example, the sample for Asian participants is not as large as other racial/ethnic groups. Fourth, this was a long survey with median completion time around 19 minutes and respondents could try to finish the survey without focusing on the questions. It is difficult to measure whether respondents read the question before answering it. However, we did implement attention filters in some of our TPB questions since they are substantially large. These filters automatically filtered out respondents who failed to provide the correct answers for each of those attention filters. Fifth, the TPB questions were hypothetical. Thus, the responses could be different for real-world scenarios. In addition, the included TPB constructs had fewer items and may not measure what it is supposed to measure. Sixth, the

Qualtrics participants are usually trained in completing survey as they get incentives from Qualtrics. Therefore, they may have the skill to complete a survey within a short period of time without much contemplating on the questions and themes. Although it is difficult to address such limitation, we confirm that there were only three respondents who completed the survey in less than 10 minutes suggesting almost all respondents may have taken adequate time to complete the survey. Finally, self-selection bias could be an issue but detailed information about the survey contents was not shared with the invitation to reduce this bias.

5.5. Future Directions and Conclusions

Future studies can use the advanced spatial analysis methods such as origin-destination (O-D) travel time matrix and 2-step virtual catchment area (2SVCA) methods to precisely measure the geographical access to genetic testing clinics in the US. Another important step could be investigating whether the listed genetic testing clinics actually provide PGx service and then analyze the geographic access to those genetic testing clinics only. Because we found that a substantial number of genetic testing clinics were not providing PGx services in a separate analysis. This calls for an updated list to examine the geographic access to genetic testing clinics. In addition, future studies can examine those states with more than 100 census tracts outside of 180-minutes driving zone to determine the factors related to the limited access. This current study only examined how travel time to genetic testing clinics varies according to one demographic factor i.e., race. Future studies can investigate the relationship between travel time and other influential demographic factors such as rurality, age, gender, and socioeconomic status etc.

Our scoping review was mostly focused on reporting barriers and facilitators using the five major CFIR domains. Findings from this scoping review revealed that most barriers and

facilitators were described in the intervention characteristics and inner settings domains. As we know that there are 39 constructs in the five domains of CFIR, this study did not examine which constructs of intervention characteristics and inner settings were most influential for genetic testing implementation. Future studies can differentiate the best practices to genetic testing implementation from poor or mediocre ones through identifying the necessary constructs. Prospective studies can also study whether there are implementation-related factors more pertinent to the US sites compared to the international settings. It is unknown whether all healthcare centers that implemented genetic testing services shared their experiences using published literatures. More institutions should come forward to participate in scientific discussions around the implementation process as well as barriers and facilitators of implementation.

Our aim 3 study findings were stratified by race-ethnicity and rurality only. We aim to examine the study results based on other demographics such as gender, age, socioeconomic status, and types of insurance. Since a large portion of our survey respondents had comorbid conditions including high blood pressure (n = 645), anxiety (n = 427), depression (n = 419), and diabetes (n = 252), future studies can look at these population groups and assess their attitude, preferences, and perceptions particularly to identify whether any differences exist. Future studies can also examine the rural population, overall and by demographics, in a separate analysis to understand their perception toward genetic testing concepts and strategies. We did observe that there were less participants from certain states. Future surveys can ensure recruiting adequate participants from all the states to increase the external validity. Investigating whether perceived behavior control and social norms moderate the relationship between attitude toward and intention to get genetic testing was not the objective of this study. It would be interesting to see

whether these determinants act as moderators for all these different disease conditions. Most importantly, educational resources should be available for all public to gauge their interest in pharmacogenetic testing regardless of their demographic characteristics. People may have different understanding of genetic testing for different diseases. Appropriate education contents targeting specific disease conditions should be prepared to address this issue. These resources should also be targeted towards specific racial and ethnic groups as well as the rural residents. Also, since online genetic testing is becoming more popular over time, regulatory agencies should be careful about the privacy and ethical concerns associated with genetic testing.

Overall, access to genetic testing clinic is still a hurdle for people living in some specific states as well as Whites compared to Blacks and Asians living in the US. Barriers and facilitators identified in this scoping review should act as a checklist for the future implementations since the findings are comprehensive and reported based on an implementation framework. Clear guidelines from the payers are required to resolve the cost and reimbursement issues to facilitate genetic testing implementation. More educational resources and trainings are required for all different stakeholders including prescribers, pharmacists, and patients to increase genetic testing uptake among general population in the US.

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