Population Genetic Screening in Adults: Implementation and Health Equity Considerations

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Abstract

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Population genetic screening among adults has been suggested as a strategy to identify people at risk for adult-onset diseases or disorders of cancer and high lipids who would benefit from early preventive intervention, but who are often missed under current genetic testing guidelines. Considering implementation challenges and health equity in population genetic screening programs is essential to ensure that screening leads to health benefits and existing health disparities are not perpetuated or widened. This dissertation examines disparities in, and barriers to, screening enrollment and subsequent preventive services, and explores health equity considerations during different population genetic screening stages. In Chapter 1, we briefly discuss motivations for population genetic screening and examples of prior screening programs. In Chapter 2, we assess enrollment in and attitudes toward population genetic screening using data from a population genetic screening research study conducted at the University of

Washington Medical Center. We found that enrollment varied by race and ethnicity and was low overall (7%), with large dropout seen during initial screening recruitment. Possible disease prevention was a shared motivator for screening among those who enrolled. We also observed three themes related to declining screening: benefits do not outweigh risks, don't want to know, and challenges with study logistics. Our results suggest that population genetic screening programs may replicate historical patterns of differential uptake of genetic services. Future programs focused on reducing logistical obstacles surrounding screening may limit these differences. In Chapter 3, we explored psychosocial impacts of learning about genetic screening results, pursuit of follow-up care, and opinions about screening among people receiving positive screening results from the population genetic screening research study conducted at the University of Washington Medical Center. We found that psychosocial impacts from screening results were limited and that participant views of result utility influenced clinical confirmation and follow-up care decision-making. After result return, many potential barriers were also present when pursuing clinical confirmation and prevention. As such, future programs would benefit from providing support not just during the initial screening process, but later in prevention stages. In Chapter 4, we identified implementation science frameworks that center health equity and assessed their applicability to population genetic screening programs. We found that frameworks provided broad guidance, including focusing on historically underserved populations, forming community partnerships, and adapting interventions to local context. However, guidance was limited for follow-up care and cascade screening stages of screening programs. Through our analysis, we created a list of health equity considerations and outcomes for population genetic screening. These considerations can be used to improve the equitable design, implementation, and evaluation of future programs. Overall, results from this dissertation

provide insight into challenges that may emerge during population genetic screening related to ensuring disease prevention and promoting health equity. Without careful consideration of such challenges, benefits from population genetic screening may be inequitably distributed.

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Chapter 1: Introduction

Advances in genetic technology and knowledge have paved the way for improvements in human health, with an increasing number of genetic tests being applied for diagnostic, pharmacogenetic, and risk estimation purposes.[1] In the United States, over 2.5 million adults are estimated to carry a pathogenic genetic variant that substantially increases their risk for serious, but preventable disease.[2] Early detection of these variants combined with medical intervention can aid in disease treatment and mitigation, and even prevent disease entirely.[3,4]

Medical guidelines recommend genetic testing for these pathogenic variants among individuals with a strong family history of related conditions.[5,6] However, at present, many at-risk individuals and families are not aware of their risk status.[7] This may be due to difficulties ascertaining family history, lack of relevant family history, and limited knowledge about and access to genetic services.[2,8]

Population genetic screening, or genetic testing of members of the population regardless of personal of family history of disease, has emerged as a strategy to improve the reach of genetic services and ascertainment of at-risk individuals who would benefit from established health interventions.[9] Recommendations for population genetic screening programs have focused on high-penetrance genes, where links to disease are well understood and effective medical interventions are available for disease mitigation or prevention.[10] These genes are primarily associated with three conditions that the Centers for Disease Control and Prevention (CDC) considers Tier 1 Genomics Applications: Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Lynch Syndrome (LS), and Familial hypercholesterolemia (FH).[7] Early detection of individuals at risk for these conditions and subsequent intervention has the potential to reduce morbidity and mortality, leading to a significant positive impact on public health.[7]

Pilot population genetic screening programs in the United States have already demonstrated the effectiveness of screening for identifying individuals at risk for Tier 1 associated conditions who may otherwise go undetected. This includes the Healthy Nevada Project, a population health study that has screened Nevada residents for pathogenic variants related to HBOC, LS, and FH and observed that 90% of the risk carriers found through screening had not been previously identified.[11] Similarly, the Geisinger MyCode Community Health Initiative (MyCode), a biobank linked to the electronic health record, found that 87% of participants identified with Tier 1 results through genetic screening did not have prior knowledge of their genetic diagnosis.[12]

Despite the public health promise of population genetic screening, there are numerous considerations to address before population genetic screening is ready for widespread implementation. Past screening projects that have taken place using biobanks, such as MyCode[12] and Bio*Me*[13] (a Mount Sinai Health System electronic health record-linked biorepository), have reported high interest and enrollment in genetic screening, with more than 80% of people approached about genetic screening in these contexts providing consent.[13,14] Yet, there is a need to determine the acceptability of genetic screening among people who are not already enrolled in genetic research and the feasibility of a population-based approach when biobank samples are not readily available for screening. Screening studies like the Healthy Nevada Project[11,15] and the Alabama Genomic Health Initiative,[16,17] a state-funded population screening program for adult Alabama residents, have begun to explore these questions but data from populations of different demographic backgrounds is currently limited.

Additional data is also needed to learn more about appropriate screening program design, including the effectiveness of different recruitment and sample collection strategies for

increasing the number of at-risk individuals identified through screening. Pilot programs have begun to experiment with pop-up screening enrollment clinics with on-site sample collection,[17] and offering screening through primary care providers.[18,19] However, continued efforts are needed to understand the costs and benefits of these various approaches.

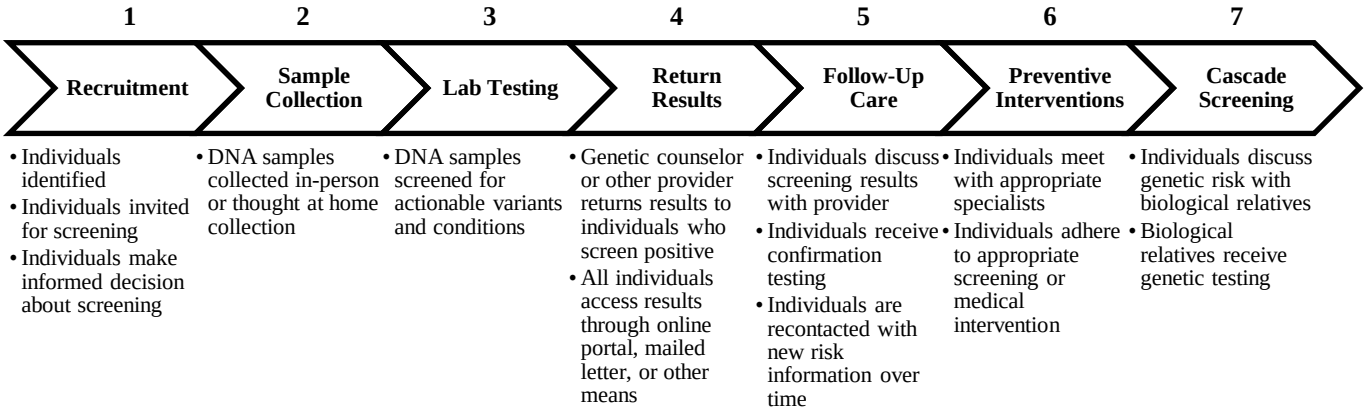
Other questions such as what the right age is for screening, who should pay for screening, if health behaviors and outcomes change due to screening results, and if any unintended harms stem from screening all require investigation.[10] Another issue of chief importance is health equity.

The World Health Organization defines health equity as the "absence of unfair and avoidable or remediable differences in health among population groups defined socially, economically, demographically or geographically."[20] Achieving health equity requires paying special attention to those at greatest risk of poor health outcomes due to social determinants including, but not limited to, race, ethnicity, religion, socioeconomic status, education, occupation, age, mental health, sexual orientation, gender identity, geographic location, and/or disability.[21]

It is essential to design and implement population genetic screening programs that center health equity so that existing health disparities are not perpetuated or widened.[22] At present, disparities already exist in the current application of genetic testing among high-risk families in the United States.[23] For instance, compared to White individuals, racial and ethnic minorities are less likely to have knowledge about genetic testing, be offered or have access to genetic services, or receive preventive care based on genetic results.[23-28] Additionally, financial concerns, fears that genetic information will be misused, and unmet cultural needs contribute to differences in utilization across demographic groups.[1,23,26,28]

When considering how best to implement population screening it is important to keep these existing inequities in mind and consider how disparities can be limited in the different stages of population screening depicted in Figure 1.1. This figure is intended to provide a high-level description of the steps involved in population genetic screening to promote disease prevention. Depending on the program, stages may be combined, and the details of each stage may vary. Briefly, the first four stages of population genetic screening encompass enrollment in screening and determination of genetic risk. This involves recruiting individuals for screening, collecting DNA samples, testing these samples for genetic variants, and returning results from this testing back to individuals. Stage 5, or follow-up care, encompasses individuals discussing their genetic risk results with their healthcare provider(s). For people screening positive, this stage also involves clinical confirmation testing and the addition of risk results to the electronic health record. Stage 6, preventive interventions, involves the translation of genetic risk knowledge into medical action. For individuals with positive results, this can include meetings with specialists, enhanced (i.e., more intensive, more frequent, or both) screening, or prophylactic surgery. Finally, stage 7, or cascade screening, moves beyond the individual who received screening, to encompass familial communication about genetic results and subsequent genetic testing among biological relatives, as needed.

Figure 1.1: Population genetic screening steps



This dissertation examines disparities in, and barriers to, screening enrollment and subsequent preventive services during different stages of population genetic screening. In Chapter 2, we assess how demographics are associated with participation in population genetic screening using data from a population genetic screening research study taking place at the University of Washington Medical Center (UWMC). We found that existing health disparities between race and ethnicity groups persisted in this population screening trial and many logistical obstacles inhibit screening enrollment. In Chapter 3, we explore the psychosocial impact of receiving genetic screening results, barriers to follow-up care, and opinions about population screening among participants screening positive in the population genetic screening study at the UWMC. We found that psychosocial impacts from screening results were limited but that many potential barriers exist for individuals moving from result return to clinical confirmation to engaging in prevention. In Chapter 4, we describe currently available implementation science frameworks that center health equity and are designed to assist with the translation of health interventions into practice. We additionally discuss how these frameworks can be applied to different stages of population genetic screening. Through our analysis, we found a variety of recommendations applicable during early population genetic screening stages, with limited

guidance available for later stages. Finally, we synthesized findings from our framework assessment into a list of health equity considerations specific to each stage of population genetic screening. Concluding comments, including the importance of this work for the equitable design and implementation of future genetic screening programs and questions requiring investigation before population genetic screening is ready for widespread implementation, can be found in Chapter 5.

Of note, Chapters 2 through 4 of this dissertation were written as stand-alone manuscripts, which will be submitted for journal publication (with some variations in language and framing) and have been in included here in their entirety. As previously mentioned, Chapters 2 and 3 use data collected through a population genetic screening research study conducted at the UWMC. The screening research study was led by the chair of this dissertation committee, Dr. Brian H. Shirts, and members of this dissertation committee assisted with the design of study protocol and survey data collection. University of Washington Department of Laboratory staff were responsible for carrying out study procedures, including recruitment, lab testing, survey data collection, and return of screening results. I was involved in data analysis and reporting for this study, some of which is included as part of this dissertation.

Chapter 2: Demographic differences in genetic screening enrollment among a diverse cohort of adults

2.1 Abstract

Purpose: The genetic screening research study conducted at the UWMC focused on screening adults in an unselected patient population for pathogenic variation in genes where medical guidelines are available to guide prevention. Analysis of enrollment and attitudes toward screening across race and ethnicity groups in this study can inform more equitable population screening efforts in the future.

Methods: In this chapter we analyzed screening enrollment and factors influencing screening decision-making overall and across race and ethnicity groups using recruitment and survey data. Reasons for not participating were also analyzed using content analysis.

Results: Overall, 40,855 people were invited for screening, with 2,855 (7%) enrolling. The average age of enrollees was 40 years and 60% were female. Enrollment varied across race and ethnicity groups, with the lowest enrollment among African American individuals (3.3%) and the highest among Multiracial or Other Race individuals (13%). Three themes emerged related to nonparticipation: benefits do not outweigh risks, don't want to know, and challenges with study logistics.

Conclusion: While screening studies among biobank participants have reported higher enrollment, results from our study may more closely reflect participation outcomes for stand-alone genetic screening programs directed to the general population. Future research focused on addressing logistical obstacles to enrollment and differences in enrollment in genetic screening across demographic groups are crucial for preventing health disparities in the population genetic screening space.

2.2 Introduction

Pathogenic genetic variants can substantially increase hereditary cancer and hypocholesteremia risk and contribute to a high proportion of early onset disease in the general population.[29-31] Medical guidelines recommend interventions that can prevent disease if an individual is known to carry a high-penetrance pathogenic variant.[4] However, recent studies among biobank participants and within population screening trials have shown that individuals with these variants often go unrecognized.[11,32,33] Given this under-ascertainment, there has been a push to expand genetic screening to unselected members of the population to identify a larger number of at-risk individuals.[9,34]

In addition to its potential to prevent more cases of hereditary cancer and hypercholesterolemia, population genetic screening has also been proposed as a more equitable strategy for risk identification.[9] Equity considerations are increasingly important given that disparities already exist in the current implementation of genetic testing among high-risk families in the United States. Clinical genetic testing services are underused by people in racial and ethnic minority groups due to a lack of referral by providers, limited genetic testing awareness, low diversity among medical genetic professionals, medical mistrust due to historic abuses, and unmet cultural needs.[1,23,24,26,28,35,36] Cost and insurance coverage concerns, as well as limited access to genetic services, also contribute to disparities in utilization.[23,26,28,35]

Learning why people may or may not engage in population screening is necessary to promote more equitable implementation and enrollment. Understanding how different individuals and communities engage with the screening process and their motivations for participation will provide valuable information about how future population screening efforts

may need to be adapted, such as if more education material or counseling need to be provided, or if perceived risks or cultural factors should be more thoroughly addressed.

Analysis in this chapter relies on data collected through a population genetic screening research study taking place at the UWMC. Screening in this research study focused on pathogenic variants in several genes where medical guidelines are available for prevention. There were many outcomes of interest in this research study including understanding factors influencing decision-making about screening enrollment, enrollment in screening, the effectiveness of screening for identifying individuals with new actionable findings, communication plans about genetic results after screening, and the impact of screening results on psychosocial health and health behaviors.

In this chapter, we specifically sought to examine factors influencing decision-making about and enrollment in genetic screening. In particular, we examined if these factors and enrollment varied by race and ethnicity. We also analyzed population genetic screening drop out overall and by race and ethnicity.

2.3 Methods

2.3.1 Background on the population genetic screening research study conducted at the UWMC

Study Participants

Participants for genetic screening were identified through a UWMC electronic health record (EHR) search. Potential participants were limited to adults 25 to 60 years old who had visited the UWMC at least two times in the last five years (2015-2020) to increase the likelihood that those who screened positive would be able to act on recommended prevention. People

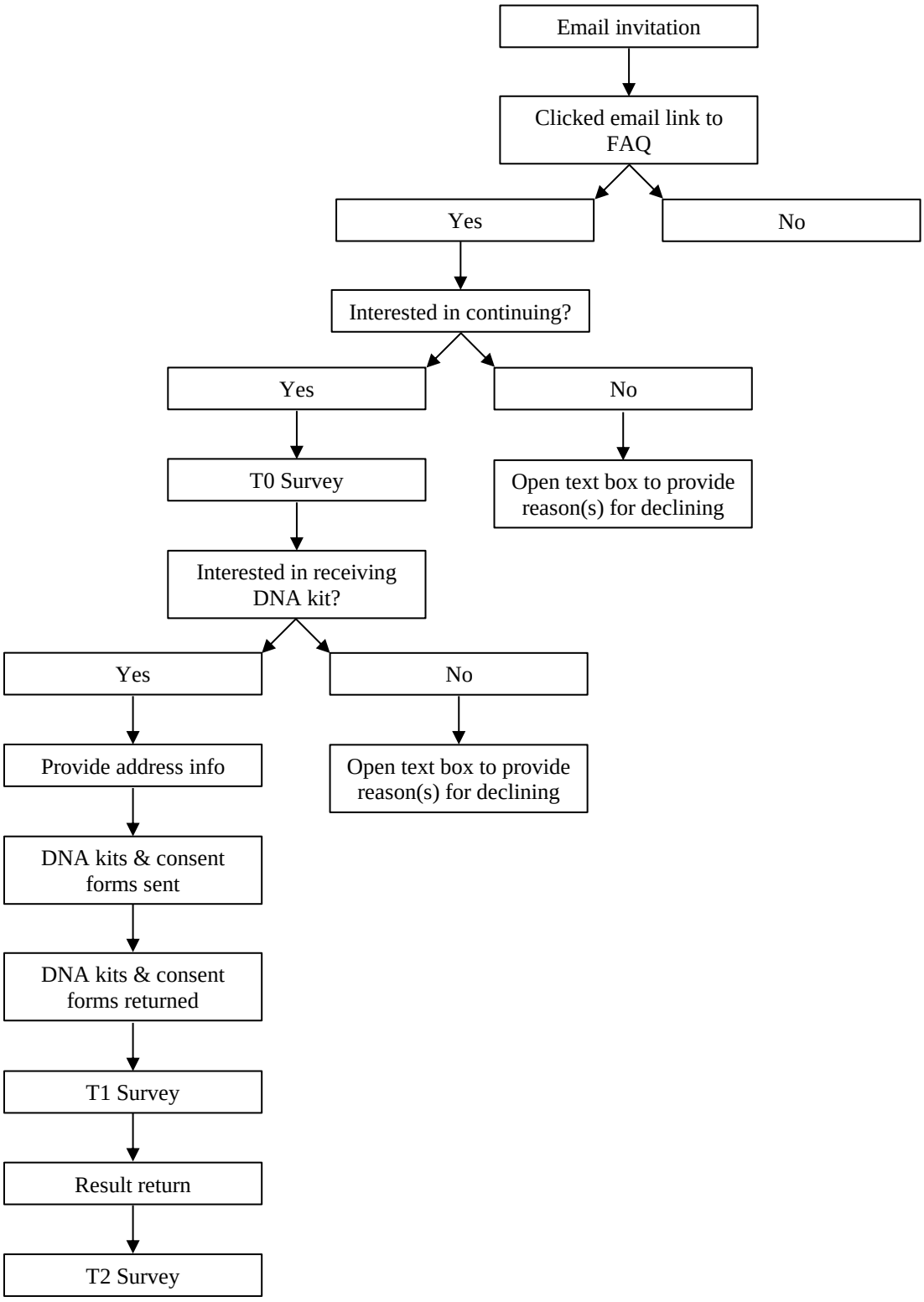
identified as racial and ethnic minorities through their medical records were preferentially selected for recruitment. A diverse group of participants was sought so that the feasibility of population genetic screening and attitudes toward this strategy could be assessed among a diverse population. Exact enrollment targets for self-identified racial and ethnic minorities were defined by research partners to meet the needs of a separate project and were 10% African American, 46% Asian, 10% Hispanic, 8% Multiracial or Other Race, 6% Native American or Pacific Islander, and 20% White, with the goal of sequencing at least 2,500 people. In order to ensure input from sexual and gender minorities, 1,000 invitations were sent to individuals self-identifying as LGBTQ+ as recorded in the EHR.

Individuals were excluded if their coded EHR information indicated previous orders for genetic testing with a hereditary cancer panel at the University of Washington Department of Laboratory Medicine or send out genetic testing ordered through the University of Washington. However, no detailed medical record review was conducted to exclude individuals who may have received genetic testing prior to entry into the University of Washington health system or testing not recorded formally in the EHR. Other than lack of prior genetic testing, no specific health profiles were specifically selected for inclusion or exclusion. Study invitations were only sent via email, and enrollment forms were only available online and in English, so those with limited access to email or the internet or unable to read English were likely to have been excluded. The study was approved by the University of Washington IRB (00009032).

Study Protocol

Overall study protocol is described in Figure 2.1 and detailed in the following sections.

Figure 2.1: Protocol for the UWMC population genetic screening study



Recruitment Email Invitations

Study invitations were sent from June 2020 to July 2021 by a study coordinator. All study automated emails with invitations and surveys were administered through REDCap. Invitations consisted of an automated email sent to potential participants containing an introductory description to the study and a link to additional research study information. People seeking to learn more about the study clicked the email link to read study information and FAQ (see Appendix), which included details about participation and study consent. Individuals who did not click on the link in the study invitation and proceed with next steps were sent up to two reminder emails about study participation at approximately one-week intervals one week after the original invitation send date.

Baseline Data Collection (T0)

At the end of the FAQ and before providing written consent, interested persons were asked if they were willing to continue (Y/N, checkbox) to answer an initial survey (T0) containing 24 close-ended questions related to personal and family medical history, factors influencing decision-making about genetic screening, and intent to share results. If "no" was selected, people were asked if they would voluntarily share their reason(s) for declining in an open text box. If "yes" was selected, they were directed to the survey.

DNA Kit Request

At the end of this baseline survey, people were asked if they would like to continue and receive an at-home DNA sample collection kit with instructions and research consent forms to join the genetic risk screening study (Y/N, checkbox). If "no" was selected, people at this stage were asked if they would voluntarily share their reason(s) for declining in an open text box. If "yes" was selected, they were asked to provide their contact and address information so a saliva-

sourced DNA kit, written study consent forms, and stamped return envelope could be mailed to their place of residence.

DNA Kit Return

Interested persons were sent an email once their DNA kit was mailed to the provided address along with electronic versions of the consent forms attached. If completed kits and consent forms were not returned within three weeks from the original send date, up to three reminder emails were sent at approximately one-week intervals to encourage completion. In some instances, a phone call from the study coordinator replaced the third, and final, reminder email.

Enrollment

Study enrollment was complete once the following were returned: DNA kit with a collected sample (via mail) and signed consent forms (via mail or electronically). For our purposes, invitees include all people who were sent study invites while enrollees include those who returned DNA samples and signed consent forms.

Post DNA Kit Return Data Collection (T1)

Once DNA kits were received in the laboratory, enrollees were notified of kit receipt via email and asked to complete an optional second survey (T1) containing a mix of close and open-ended items. This survey asked more detailed questions about personal and family medical history, demographics, intent to share results, and knowledge about genetics. The T1 survey also included specific questions relevant to genetic test interpretation and reporting, such as if enrollees had received prior genetic testing or bone marrow transplants or if they knew of others in their family who had received genetic testing results about hereditary disease risk. If the T1

survey was not completed within one week of the original send date, up to two reminder emails were sent at approximately one-week intervals to encourage completion.

Genetic Screening Panel

The screening panel described to invitees consisted of genes associated with diseases or disorders of cancer and high lipids, for which clinical procedures or therapies are available for disease prevention, mitigation, and treatment. A list of the targeted genes and their associated conditions (Table 2.1) was available on the study website.

Table 2.1: List of genes tested in the population genetic screening research study conducted at the UWMC

Gene	Associated Condition(s)
APC	Colon polyps, colon cancer
APOB	Familial hypercholesterolemia
ATM	Breast cancer
BMPR1A	Colon polyps, colon cancer
BRCA1	Breast, ovarian, and pancreatic cancer
BRCA2	Breast, ovarian, and pancreatic cancer
BRIP1	Breast and ovarian cancer
CDH1	Breast and stomach cancer
CHEK2	Breast and colon cancer
EPCAM	Colon, endometrial, and ovarian cancer
HOXB13	Prostate cancer
LDLR	High cholesterol, coronary artery disease
MLH1	Colon, endometrial, and ovarian cancer
MSH2	Colon, endometrial, and ovarian cancer
MSH6	Colon, endometrial, and ovarian cancer
MUTYH	Colon polyps, colon cancer
NTHL1	Colon polyps, colon cancer
PALB2	Breast and ovarian cancer
PMS2	Colon, endometrial, and ovarian cancer
PTEN	Colon polyps, colon cancer
RAD51C	Ovarian cancer
RAD51D	Ovarian cancer
SMAD4	Colon polyps, colon cancer
STK11	Colon polyps, colon cancer
TP53	Breast and many other cancers

Results Return

Invitees were told that screening results would be returned through an online portal unique to the research study or by a genetic counselor. For results indicating no increased risk for the screened conditions, enrollees were notified that their results were available via email and were able to access their result letter for viewing and printing on a secure and private website. Enrollees whose test indicated an increased risk for any tested disease were notified by a study

genetic counselor via email that their results were ready and asked to schedule a phone conversation with the genetic counselor to discuss these results.

While enrollees were notified that results would not be included in the EHR, they were encouraged to share their results with their own medical provider. Both the consent form and result letter stressed that medical management and/or follow-up would not occur within the research study or by research staff. The study genetic counselor was available for consultations with enrollees or their provider if this was requested.

Post Result Return Data Collection (T2)

Enrollees were asked to complete an optional post-results survey (T2) after they received their genetic screening results. If results were not returned to an enrollee (e.g., the study genetic counselor was unable to contact an enrollee to disclose positive results) then a T2 survey was not administered for completion. The T2 survey consisted of both close and open-ended items and asked about plans to share screening results, future health plans, and feelings about results and genetic screening. If the T2 survey was not completed within one week from the original send date, up to two reminder emails were sent at approximately one-week intervals to encourage completion. After this point, data collection for the population genetic screening study concluded.

2.3.2 Survey measures of interest for enrollment analysis

Demographic data, including age, gender, race, and ethnicity, were available for all study invitees through the UWMC EHR. EHR gender categories included female, male, and other/unknown. EHR race categories included African American, Asian, Caucasian (referred to as White hereafter), Multiracial/Other, and Native American, and ethnicity categories included Hispanic and Non-Hispanic. The T1 survey also asked about gender, race, and ethnicity. When

asked about gender, respondents were asked to select one of the following choices: female, male, other, prefer not to answer. When asked about race, respondents could select one or more of the following choices: Alaska Native, American Indian, Asian, Black/African American, Native Hawaiian, Other Pacific Islander, Other race, White, Prefer not to answer, and Don't know. In a separate question, respondents were also asked if they identified as Hispanic (Yes/No). As T1 survey data was not reported for all invitees, EHR demographics were used for subsequent analyses to maximize available data. However, individuals who selected "Prefer not to answer" for the gender question in the T1 survey were classified as such during subsequent analyses to respect potential desires to refrain from reporting gender.

We defined enrollment in this study as the return of DNA samples and signed consent forms. Detailed demographic and health data for study enrollees was gathered from the T0 and T1 surveys. T0 characteristics of interested included if enrollees were adopted, had a personal diagnosis of cancer, a diagnosis of cancer in the family, had ever experienced a heart attack or had a family member experience a heart attack. Family in these questions was defined as a close biological relative, such as a mother, father, son, daughter, aunt or uncle. T1 characteristics of interest included sex assigned at birth, sexual orientation, education, income, any past genetic testing, or any genetic testing in the family indicating an increased disease risk. Similar to the T0 survey, the T1 survey also asked about personal and family history of cancer or heart attack and proceeded to go into more detail to learn exactly which family members had experienced these conditions. However, because T1 survey completion was lower compared to T0 and detailed family history information was not the focus of this analysis on screening enrollment, T0 data was used to report personal and familial cancer and heart attack status.

Given our interest in screening enrollment, analysis in this chapter also drew from T0 survey questions where people were asked about factors influencing their decision-making about genetic screening using a scale adapted from Fraint et al.[37] For a series of 16 statements (Table 2.2), respondents were asked to indicate how important the given statement was in their decision-making using a Likert scale (not important at all, somewhat important, very Important, not applicable).

Table 2.2: Items used to assess factors influencing decision-making about genetic screening

To learn that I do not have an inherited disease risk gene
To make decisions about having (more) children
To alter priorities (personal, career, etc.) if an inherited disease risk is present
To be able to psychologically prepare myself for what lies ahead if the test reveals that I have inherited disease risk
If the test reveals that I have an inherited disease risk, I would want it to be identified early on so that I can prevent or treat the disease
I will regret taking the test if an inherited disease risk is identified
Participating in genetic testing is against my personal moral code
Knowing whether I have an inherited disease risk would not change what I would do in life
There is no effective cure/treatment for most genetic disease
I need to know more about the test
I want to know the test is accurate enough
My family thinks that I should or should not have genetic testing
I want to know if my healthcare provider thinks that I should or should not have genetic testing
I am worried that the results will not remain confidential
I am worried about losing my health insurance
I am afraid that I would lose my job or be discriminated by future employers

2.3.3 Analysis

We calculated the number of study invitees and enrollees and descriptive statistics using EHR demographic data for study invitees and enrollees separately. We also descriptively

assessed overall drop out in this screening study by looking at the number of people who proceeded through different steps: (1) sent study invites, (2) accessed study FAQ, (3) requested a DNA collection kit, (4) sent a DNA collection kit and consent forms, (5) returned DNA sample and signed connect forms. In addition, we also descriptively assessed drop out between these steps by race and ethnicity.

We used two logistic regression models to examine the association between race and ethnicity and enrollment in population genetic screening. Model A included age (linear), gender (Male, Female, Other), and race/ethnicity (ascertained from the EHR: Hispanic (of any race), Asian [reference], African American, Multiracial/Other, Native American, White (latter 5 categories were all Non-Hispanic) as covariates. Model B additionally included a gender by race and ethnicity interaction term as differences in engagement in genetic services and research has been seen based on gender and race and ethnicity.[1,38,39] We investigated significant interaction effects by calculating the probability of enrollment for individuals in groups relevant to the interaction using the mean age of invitees. We also conducted an exploratory analysis to assess the relationship of sexual orientation (a binary variable indicating if an individual was in the group of 1,000 LGBTQ+ invitees as coded in the EHR) with study enrollment by adding sexual orientation and a sexual orientation by race and ethnicity interaction term as additional covariates to the original Model A. Individuals who had selected "Prefer not to answer" for questions regarding gender in the T1 survey were excluded from these analyses.

We descriptively analyzed the T0 survey data regarding factors influencing decision-making about screening to see which factors were most important and least important. We also used a Kruskal Wallis test to assess if enrollees from different race and ethnicity groups (ascertained from the EHR) responded differently to these survey questions. We excluded "Not

Applicable" and skipped/missing responses from this analysis and applied the Holm method[40] to correct for multiple testing with an alpha level of 0.05. As the T0 survey was primarily completed by people who went on to enroll in screening, this analysis was restricted to enrollees. However, enrollees did not need to have completed subsequent surveys (T1 or T2) to be included in this analysis. All statistical analyses were conducted in R version 3.6.1.

As many of our analyses relied on EHR race and ethnicity, which has been reported to contain inaccuracies,[41] we compared EHR race and ethnicity to survey self-reported race and ethnicity to inform interpretation of enrollment analysis results.

Finally, we analyzed survey open text box responses about reasons for declining study enrollment using an inductive content analysis approach.[42] We also calculated counts related to each theme to indicate the relative strength of ideas. Comments were exported from REDCap into Excel for analysis. All comments were analyzed together and not separated based on the EHR race or ethnicity of the person who provided them. A primary coder (NDR) created a codebook and performed the initial coding. These codes were verified by a second coder (BHS) and code definitions and applications were refined through discussion. Both coders reviewed all text responses and codes, and all discrepancies were resolved through discussion.

2.4 Results

Study Demographics, Participation, and Drop Out

A total of 40,855 people were invited to participate in the population genetic screening research study conducted at the University of Washington Medical Center, with 2,855 (7%) people enrolling. On average 3,100 study invitations were sent each month of the study to meet the goal of over 2,500 total people screened. Age, gender, race and ethnicity information of all invitees and for enrollees only are provided in Table 2.3. The average age of all invitees and

among enrollees was 40 years. While 54% of invitees were female, approximately 60% of enrollees were female. Within enrollees, 57% were Asian, 12.3% African American, 6.2% Native American, 0.8% Multiracial or Other Race, and 23.2% White.

Table 2.3: Electronic health record demographics of study invitees and enrollees

	Invitees	**Enrollees**
N	40855	2885
Age[a]	40 (10.2)	40 (10.0)
Gender[b]		
Female	22205 (54.3)	1717 (59.5)
Male	18537 (45.4)	1098 (38.1)
Other	81 (0.2)	50 (1.7)
Prefer not to answer	32 (0.1)	20 (0.7)
Race[b]		
African American	10639 (26)	354 (12.3)
Asian	22042 (54)	1645 (57.0)
Multiracial/Other	177 (0.4)	23 (0.8)
Native American	2543 (6.2)	180 (6.2)
White	5436 (13.3)	670 (23.2)
Missing	18 (0.1)	13 (0.5)
Ethnicity[b]		
Hispanic	4098 (10)	368 (12.8)
Non-Hispanic	36738 (89.9)	2504 (86.8)
Missing	19 (0.1)	13 (0.4)

[a]Mean (SD); [b]N (%)

Detailed information about enrollees, including health history, education, and income are listed in Table 2.4. Among enrollees, 53% of people had a family history of a cancer diagnosis, approximately 60% reported having a college or advanced degree, and 38% reported a household income greater than $100,000.

Table 2.4: Detailed demographics of enrollees

Characteristic	N (%)
Adopted	
Yes	114 (4.0)
No	2759 (95.6)
Missing	12 (0.4)
Personal cancer diagnosis	
Yes	321 (11.1)
No	2556 (88.6)
Missing	8 (0.3)
Family cancer diagnosis[a]	
Yes	1534 (53.2)
No	1021 (35.4)
Don’t know	318 (11.0)
Missing	12 (0.4)
Personal heart attack[b]	
Yes	42 (1.5)
No	2832 (98.1)
Missing	11 (0.4)
Family heart attack[a]	
Yes	1008 (34.9)
No	1326 (46.0)
Don’t know	544 (18.9)
Missing	7 (0.2)
Sex assigned at birth	
Male	762 (26.4)
Female	1295 (44.9)
Other	0 (0)
Prefer not to answer	3 (0.1)
Missing	825 (28.6)
Sexual orientation[c]	
Asexual	84 (2.9)
Bisexual	147 (5.1)
Gay or lesbian	171 (5.9)
Queer	77 (2.7)
Straight	1558 (54.0)
Something else	20 (0.7)
Don’t know	10 (0.4)
Prefer not to answer	42 (1.5)

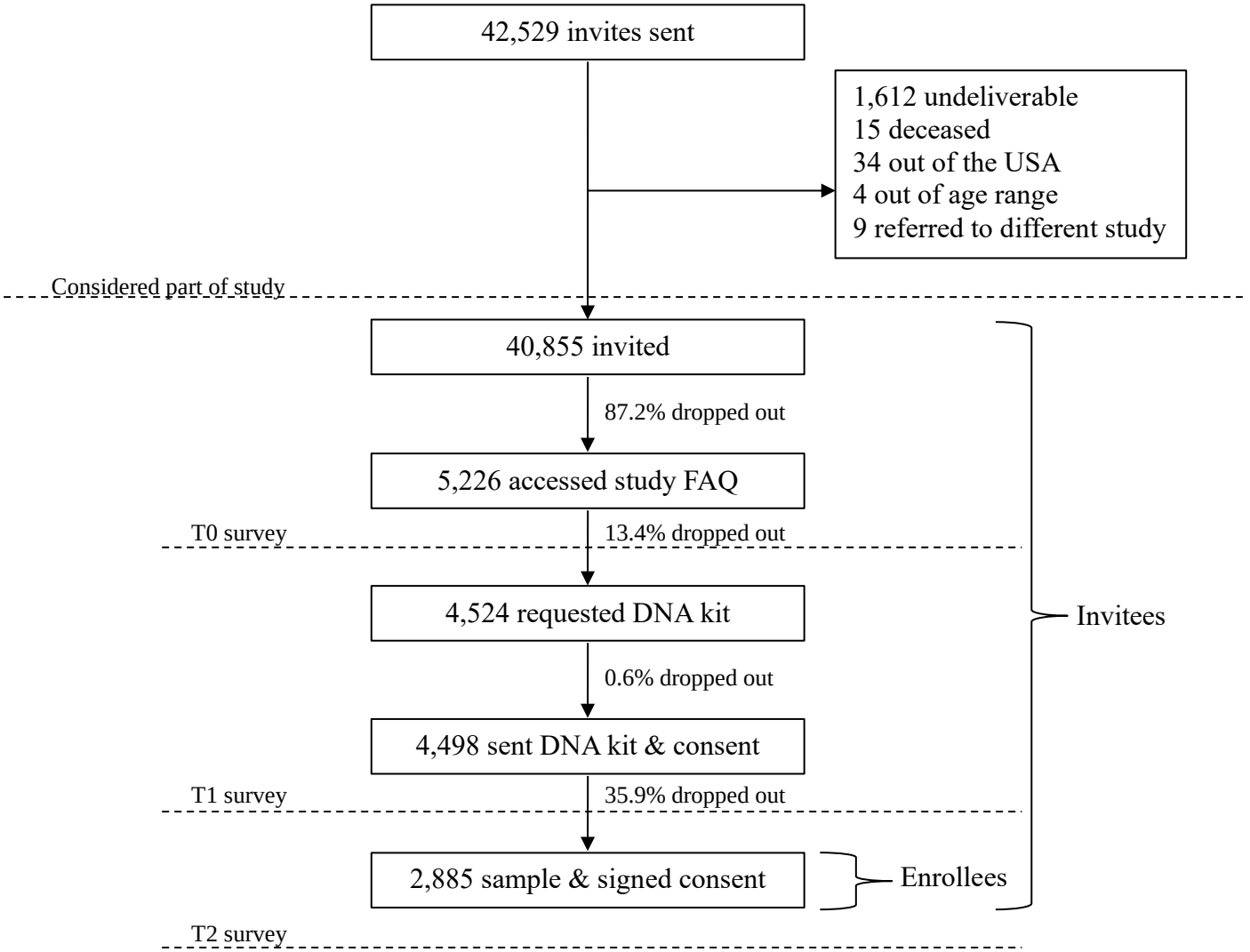
Missing	840 (29.1)
Education	
Less than high school	6 (0.2)
High school/GED	60 (2.1)
Some college	299 (10.4)
College graduate	863 (29.9)
Advanced degree	887 (30.7)
Missing	770 (26.7)
Household Income	
<$50,000	301 (10.4)
>$50,000 but ≤100,000	539 (18.7)
>$100,000	1104 (38.3)
Prefer not to answer	191 (6.6)
Missing	750 (26)
Past genetic testing	
Yes	425 (14.7)
No	1686 (58.5)
Missing	774 (26.8)
Family genetic testing showing increased risk[d]	
Yes	99 (3.4)
No	1956 (67.8)
Missing	830 (28.8)

[a]Family was defined as a close biological relative (mother, father, son, daughter, aunt, uncle)
[b]At any point in time
[c]Multiple choices could be selected
[d]Degree of relatedness was not specified in question. This question was asked to all people administered the T1 survey and a not applicable option to indicate a lack of family genetic testing was not provided

Figure 2.2 shows how people moved throughout the study, including reasons people were unable to be recruited for screening and when dropout occurred. Email invitations for screening were undeliverable in 1,612 (3.8%) instances. Overall, the greatest amount of study dropout occurred during the early stages of recruitment as 87.2% of invitees did not click on the link in the email study invitation to learn more about the study. Of the people who did access the study FAQ, 13.4% did not request a DNA kit for sample collection after reading more about the screening study. Larger dropout was also seen after people were sent DNA kits for sample

collection and study consent forms, with 35.9% of people sent collection kits and consent forms not completing collection or signing forms to proceed with screening.

Figure 2.2: Study participation at different stages of population screening



Trends in study involvement and dropout for all invitees and across race and ethnicity groups are shown in Figure 2.3 and are detailed in Table 2.5. A higher percentage of Multiracial or Other identifying individuals continued to access the study FAQ compared to other groups, with African American individuals having the highest percentage of dropout at this stage

compared to other groups. Dropout trends remained relatively consistent across groups for the remainder of the study. Between when DNA sample collection kits and consent forms were sent out and returned, the greatest dropout was seen for Multiracial or Other Race individuals and Native American individuals.

Figure 2.3: Study drop out by race & ethnicity

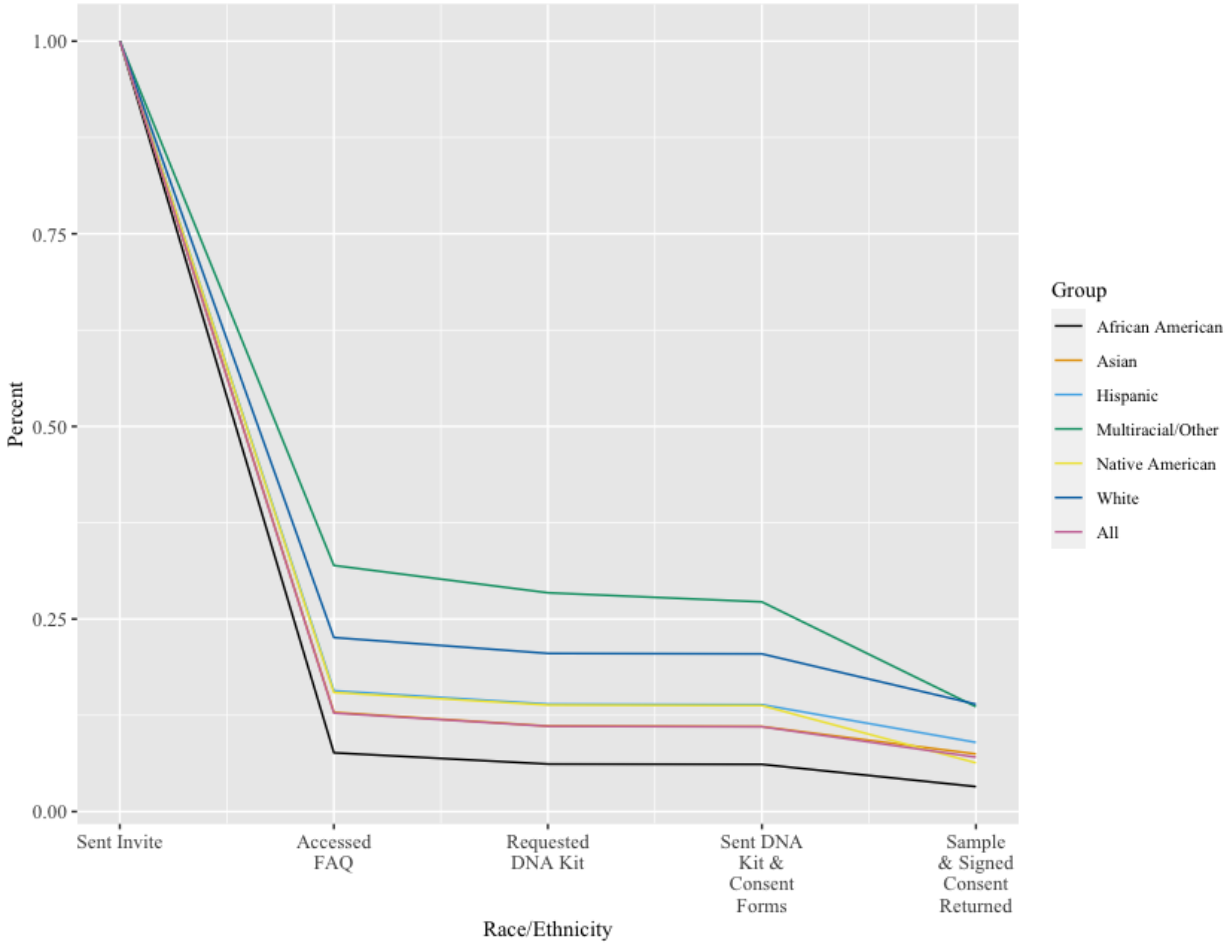


Table 2.5: Study participation at different stages of population screening by race and ethnicity [N (%)]

	Overall	African American	Asian	Hispanic	Multiracial/ Other	Native American	White	Missing
Invited	40,855 (100)	10,267 (100)	21,706 (100)	4,098 (100)	169 (100)	1,533 (100)	3,063 (100)	19 (100)
Accessed FAQ	5,226 (13)	784 (8)	2,798 (13)	643 (16)	54 (32)	237 (15)	692 (23)	18 (95)
Requested kit	4,524 (11)	634 (6)	2,411 (11)	572 (14)	48 (28)	212 (14)	629 (21)	18 (95)
Sent kit	4,498 (11)	630 (6)	2,397 (11)	569 (14)	46 (27)	211 (14)	627 (21)	18 (95)
Sample & signed consent returned	2,885 (7)	333 (3)	1,624 (7)	368 (9)	23 (14)	97 (6)	427 (14)	13 (68)

Associations were detected between EHR race and ethnicity and enrollment in the screening study. After adjusting for age and gender, results from logistic regression Model A (Table 2.6) showed that African American individuals had lower odds of enrollment compared to Asian individuals [OR: 0.41, 95% CI: (0.36, 0.46)]. White, Multiracial or Other Race, and Hispanic individuals had higher odds of enrollment compared to Asian individuals [OR: 1.81, 95% CI: (1.61, 2.04); OR: 1.75, 95% CI: (1.1, 2.79); OR: 1.21, 95% CI: (1.07, 1.36), respectively]. Enrollment odds did not significantly differ between Native American and Asian individuals.

Table 2.6: Association of race & ethnicity with enrollment

Race/Ethnicity	Beta	SE	P-Value	OR (95% CI)
African American	-0.90	0.06	<2e-16	0.41 (0.36, 0.46)
Hispanic	0.19	0.06	0.002	1.21 (1.07, 1.36)
Multiracial/Other	0.56	0.24	0.018	1.75 (1.1, 2.79)
Native American	-0.19	0.11	0.072	0.82 (0.67, 1.02)
White	0.59	0.06	<2e-16	1.81 (1.61, 2.04)

*adjusted for age (continuous) and gender (male, female, other); Asian as reference

Results from Model B showed a significant interaction with male gender and African American race (p=0.003), such that odds of enrollment were lower for African American men compared to African American women. Similarly, a significant interaction was also seen with male gender and Hispanic ethnicity (p=0.009), such that odds of enrollment were lower for Hispanic men compared to Hispanic women.

Table 2.7 lists the predicted probability of enrollment for groups implicated in these interactions assuming an age of 40 years. These estimates suggest that 40-year-old African American men were less likely to enroll in screening compared to African American women of the same age (0.03 vs. 0.04, respectively). Additionally, 40-year-old Hispanic men were also estimated to be less likely to enroll in screening compared to Hispanic women of the same age (0.07 vs. 0.11, respectively).

Table 2.7: Probability of study enrollment for men and women aged 40 in race and ethnicity groups where a significant interaction was present with gender and race and ethnicity

	African American	Asian	Hispanic
Female	0.04	0.08	0.11
Male	0.03	0.07	0.07

Asian as reference

Exploratory analyses adding sexual orientation and an interaction with sexual orientation and race and ethnicity as covariates to Model A showed that there was no independent association between sexual orientation and enrollment. As such, results from this analysis are not shown here.

Survey questions about factors influencing screening decision-making were completed by 99.5% of enrollees (n=2,872). Responses showed that learning about disease risk and identifying risk early for prevention purposes were important factors in decision-making to receive screening (Figure 2.4). Mental preparation, altering priorities, and test accuracy were factors of moderate importance in decision-making. Overall, regrets about screening and screening being against one's moral code were not viewed as important. Provider and family opinion were also limited in perceived importance.

Results of the Kruskal-Wallis test indicated that the distribution of survey responses regarding factors influencing screening decision-making were significantly different across race and ethnicity groups for all questions after applying the Holm method for multiple comparison (Table 2.8). The lowest p-values were seen for statements concerning test accuracy ($p < 2.2E-16$) and needing to know more about the test ($p < 2.2E-16$). Compared to other enrollees, African American and Asian enrollees considered these factors to be of greater importance.

Figure 2.4: Factors that influence decision-making about genetic screening enrollment across race and ethnicity groups

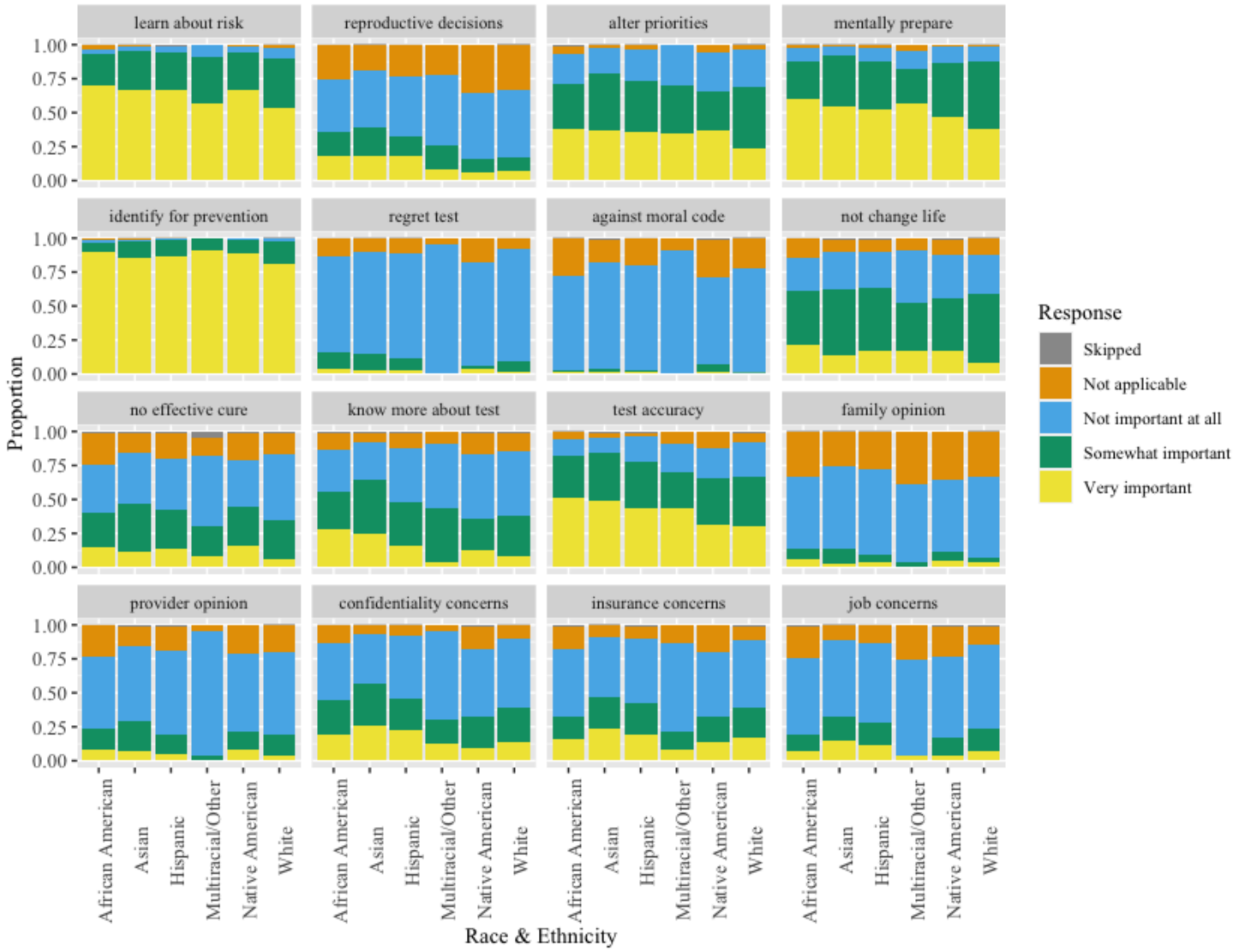


Table 2.8: Assessing differences in factors influencing decision-making about genetic screening enrollment across race and ethnicity groups

(all p-values considered significant after correcting for multiple comparisons)

Statement	Kruskal-Wallis P-value
To learn that I do not have an inherited disease risk gene	1.18E-06
To make decisions about having (more) children	1.00E-11
To alter priorities (personal, career, etc.) if an inherited disease risk is present	1.88E-05
To be able to mentally prepare myself for what lies ahead if the test reveals that I have inherited disease risk	2.12E-08
If the test reveals that I have an inherited disease risk, I would want it to be identified early on so that I can prevent or treat the disease	0.006
I will regret taking the test if an inherited disease risk is identified	0.002
Participating in genetic testing is against my personal moral code	0.004
Knowing whether I have an inherited disease risk would not change what I would do in life	0.013
There is no effective cure/treatment for most genetic disease	1.72E-05
I need to know more about the test	<2.2E-16
I want to know the test is accurate enough	<2.2E-16
My family thinks that I should or should not have genetic testing	0.016
I want to know if my healthcare provider thinks that I should or should not have genetic testing	3.18E-06
I am worried that the results will not remain confidential	2.09E-12
I am worried about losing my health insurance	8.98E-05
I am afraid that I would lose my job or be discriminated by future employers	1.52E-06

Comparison between UWMC EHR race identification and self-reported race from T1 survey data collection showed that the relationship between the two is complex (Figure 2.5) and that racial identity varies depending on how it is ascertained. In particular, the EHR had limited race categories compared to the T1 survey and individuals could only fall into only one EHR classification. In contrast, enrollees could select multiple races in the T1 survey and 56% of enrollees did so.

Though ethnicity was captured in the T1 survey in a similar fashion to the EHR, there were still some inconsistencies, with 5% of people classified as Hispanic in the EHR selecting Non-Hispanic in the T1 survey, and 1% of people classified as Non-Hispanic in the EHR self-reporting as Hispanic in the T1 survey (Figure 2.6).

Given the complexity of the relationship between EHR race and ethnicity and survey EHR race and ethnicity, results from the analyses presented previously should be interpreted cautiously. While overarching considerations and patterns may hold, specific conclusions may be difficult to draw due to the challenges of ascertaining race.

Figure 2.5: EHR race vs. survey-reported race

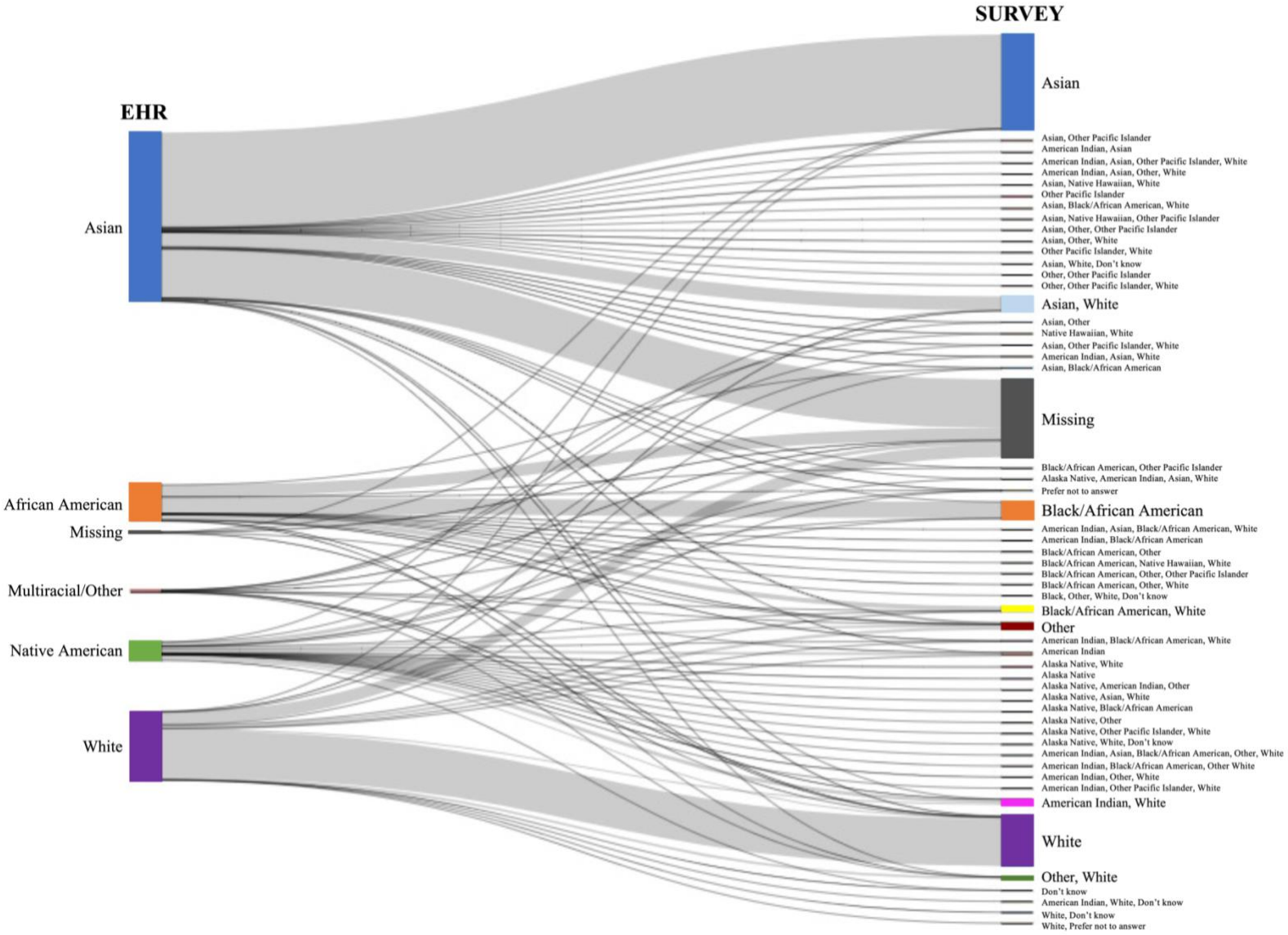
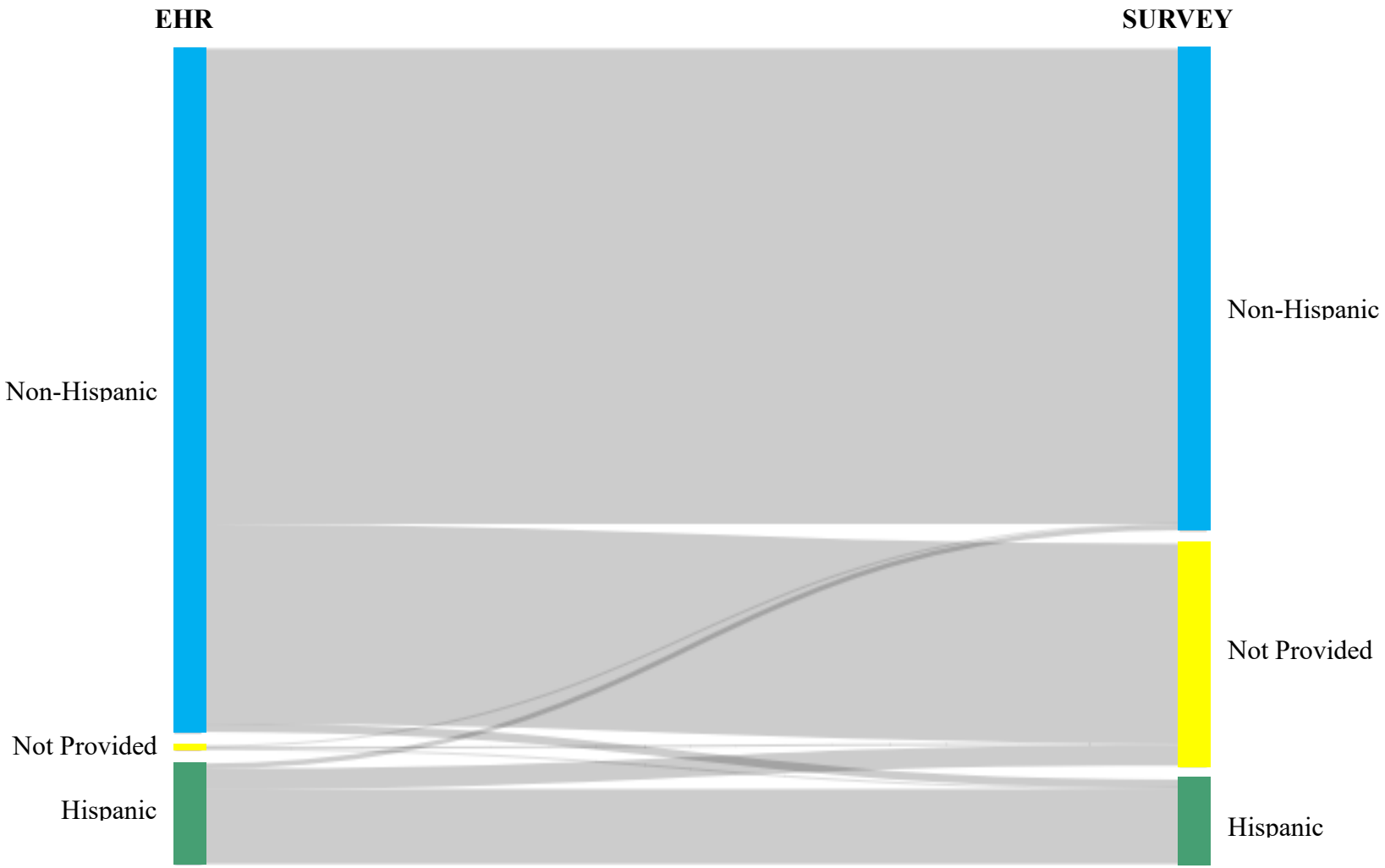


Figure 2.6: EHR ethnicity vs. survey-reported ethnicity



Reasons for Non-Enrollment

One hundred thirty-nine people (0.4% of non-enrollees) provided survey open text box responses describing why they were not interested in receiving screening (either before or after the T0 survey). Among these responses, 3 main themes were observed.

Benefits don't outweigh risks

Many people shared that while they found the study interesting, the proposed benefits did not seem worthwhile enough given the potential risks. Among the risks described were concerns related to loss of insurance or employment, privacy, and security of genetic data and samples. While the Genetic Information Non-Discrimination Act's protections against genetic discrimination in health insurance and employment were described in the study FAQ, the FAQ also indicated that the study could not guarantee those protections. Twenty-five percent of respondents (35/139) noted fears about genetic discrimination with one person sharing:

> While I want to know about my genetic risk, the personal risk to genetic discrimination is too great due to the history of private health insurers denying coverage for pre-existing conditions. Their behavior demonstrates that they will do everything possible to deny coverage for any reason. – *ID#37030, Male, 49*

Some expressed concerns that data would not remain secure and could potentially be misused in the future leading to personal harm or harms for future generations (34/139). For example, one person noted that they were worried about their data remaining safe and described their reasons for not enrolling as:

> Concerns about personal info safety. DNA profiling and characterization is such a sensitive issue, any leak of info, whether here or down the road could lead to potentially serious outcomes. – *ID#18527, Female, 34*

Others echoed concerns that genetic data would end up in the hands of third parties and used for purposes other than what was described in the study. One person shared:

> I am concerned my DNA could become available to a third party either as the result of legal action or unauthorized access (e.g., hacking). – *ID#20058, Male, 54*

Don't want to know

Non-enrollees also indicated they did not want to know about genetic risk because of concerns over usefulness (20/139), and the emotional burden (11/139) of possible results. Despite the study FAQ describing that positive results would need to be confirmed by clinical testing and the study's focus on genetic risk results with medical guidelines available for prevention, some expressed concerns about what could be done with the risk information that they might receive. For example, one person described not knowing if any action could be taken:

> Right now, I am not sure what can be done even if some genetic factors may cause certain diseases. It is better not knowing so life can be normal. – *ID#5678, Male, 60*

Others shared that the information would not necessarily be useful given their personal circumstances:

> Just decided that at my age it really doesn't matter and I already pretty much know my family history – *ID#46319, Female, 60*

People also expressed concerns about the stress of finding out about genetic risk results, particularly when already dealing with so many other life stresses.

> I don't want the emotional burden of knowing my risk factors for disease. I'd rather just live as healthy as I possibly can knowing I am maximizing my chances of longevity. The added knowledge of risk will be too much pressure and stress which is not conducive to healthy habits, I've found. – *ID#31326, Female, 37*

> I would worry too much waiting for results and then once results arrive worry about issues found if there were any. The worry would be bad for my health. I may change my mind in a year or two, but now with all that is going on with Covid and the political climate, I can't take on another item. – *ID#2755, Female, 59*

Challenges with study logistics

Finally, people noted concerns with the study process itself that were preventing them from enrolling. The biggest issue was a lack of compensation for joining and sharing personal genetic data, which was expressed by 28/139 (20%) of non-enrollees providing comments:

> I think it is not completely fair that I don't get paid for my time and effort. – *ID#27586, Male, 32*

> My DNA and No money? Think again! – *ID#35255, Male, 28*

Some also expressed issues with the at-home sample collection process. For example, one person shared:

> I thought this would be a blood test done at the UWMC. I don't want to be responsible for collecting and mailing in saliva myself. – *ID#36972, Female, 59*

Given the email study invitation and at-home nature of the study, there were also concerns about the legitimacy of the study and how people were selected for recruitment. One person commented:

> This seems like a scam. Sure I can call [Study PI] but then you would also have my number. How did you get my email contact. – *ID#14099, Female, 27*

Other logistical inconveniences noted by non-enrollees included a lack of time, having moved or currently moving out of the area, and ongoing health treatments making it difficult to enroll.

2.5 Discussion

Our analysis reflects enrollment outcomes in genetic screening using an email, invitation-based recruitment approach and demonstrates challenges that may emerge if screening were implemented as a stand-alone program. Differences in enrollment were present across race and ethnicity groups. Across groups, learning about inherited disease risk for prevention purposes was a primary motivator for enrolling but reported barriers to enrollment were concerns about risks, including discrimination and data privacy, the emotional burden of results, and challenges with study logistics. High study dropout after screening invites were sent and after DNA kits were mailed out for sample collection also indicate procedural issues that inhibit enrollment.

Enrollment in our genetic screening trial was lower than that reported by previous population genetic screening studies. Among new participants of the Bio*Me* Biobank, 93.4% indicated that they wished to receive genetic results.[13] It is possible that because those participants were those already inclined to join a biobank, they may have been more amenable to research participation and interested in genetic findings generally. The Geisinger MyCode community health initiative, a biobank linked to the electronic health record, has also seen high levels of engagement, both for enrollment in the research biobank and for return of genetic

results.[14] More than 85% of people approached about MyCode have consented to participation.[14] The integration of this program into existing healthcare practices is likely a large contributor to enrollment, suggesting that incorporation of genetic screening into routine care may improve enrollment overall. This is echoed by results from DNA10K, a population genetic screening program mediated by primary care providers, that reported that 77% of patients who were contacted about genetic screening had an order placed by their provider.[18] Therefore, results from our study may more closely reflect enrollment outcomes if screening were implemented among an unselected population as part of a stand-alone public health initiative and suggests that enrollment in genetic screening may be improved by incorporating programs into existing health systems.

Our results appear to replicate historical patterns of differential use of genetic services and highlights the need to gather pilot population genetic screening data from the general population that recognizes geographic, socioeconomic, education, gender, sexual orientation, and racial and ethnic diversity. The Healthy Nevada Project[15] and Alabama Genomic Health Initiative (AGHI)[17] have both seen success in recruiting individuals from different racial and ethnic backgrounds. Those programs engaged in a variety of outreach efforts using mass media, public events, multiple site enrollment and community partnerships,[15,17] rather than exclusively email-based recruitment, as for our study. Therefore, more personal enrollment tactics and involvement with the community may be required to better engage racial and ethnic minority groups. In particular, the AGHI has been able to increase African American participant enrollment over the course of their screening program through pop-up enrollment clinics, which improve awareness and access to enrollment by reducing logistical obstacles and bringing

information directly to communities.[17] On-going and long-term efforts to build trust through stakeholder engagement have also been shown to aid recruitment efforts.[43]

Implementing population screening is a challenging multi-step process with many possible stages for drop out. Our study demonstrates that several issues still need to be addressed throughout the population screening process before participation is considered a viable option for many. While our analyses were limited by the small number of people providing reasons for not enrolling, the feedback provided was informative. Enrollment barriers were similar to those seen in previous studies among high-risk individuals, including logistical issues and concerns about genetic discrimination, data misuse, emotional impact, and decision-making based on results.[44-47] Improved informed consent processes that highlight prevention possibilities may mitigate the emotional burden and health related concerns for some. However, it is likely that other individuals may still find learning about genetic risk too stressful, particularly while protections against genetic discrimination remain limited. Importantly, genetic discrimination was still a cause of concern for invitees in our study despite results not being included in the medical record. Larger study dropout between when kits were sent and returned indicates that more support is necessary during the sample collection phase of population screening to manage logistical constraints such as lost kits, moves and other difficulties with sample collection. Drop out during this period may also signal that screening is not a high priority for some individuals, despite initial interest, and that alternative modes of sample collection, such as in-person appointments, may facilitate screening in some instances.

Analysis of factors influencing screening decision-making provide insight into where adjustments can be made to future screening programs to increase enrollment. Shared motivators, such as the potential for prevention, suggest that heightened attention on addressing process

barriers to participation, can capitalize on these motivations and lead to higher enrollment. Recruitment efforts that discuss test accuracy and how results can assist with preparations for the future may also improve participation.

Limitations

Our study was limited by the amount and types of data available. In particular, many of our analyses depend on EHR classifications of race and ethnicity. While these identifications are thought to be based on self-report, we did not have data on when they may have been last updated, which choices were offered, and if identifications are ever added or altered by providers. Comparison between EHR race and ethnicity and our survey data demonstrates that these social characteristics are highly dependent on how they are measured and are therefore limited in their explanatory ability. Even among our survey data collection, categorizations remained broad. For example, Asian may encompass a wide variety of people from different geographic, cultural, and linguistic backgrounds. Such broad categories do not allow for more nuanced social identification, and it is possible that patterns exist within race and ethnicity groupings that are obscured because of current classifications. Relevant demographic factors that may influence participation, such as socioeconomic status, insurance coverage, disability status, and neighborhood, were also not available for all study invitees and therefore, were not considered here. Our results may also have been impacted by the limited recruitment of Multiracial or Other Race individuals, as indicated by the EHR. Even with limitations in racial and ethnic classification, our results illustrate that there are differences in enrollment in genetic screening between groups that need to be addressed. Overall, the racial and ethnic diversity of

this study provides valuable insight into how population genetic screening might be received among adults in the general population.

2.6 Conclusion

Though population genetic screening has the potential to identify individuals at risk for inherited conditions, differential enrollment suggests that this strategy is not a simple panacea for alleviating disparities in genetic testing and access. Broad social issues that have led to previous health disparities persist in the population screening setting and several factors may inhibit genetic screening participation. A failure to address these issues and differences in participation may exacerbate disparities in genetic services. Continued research centered on understanding attitudes toward genetic screening and removing logistical obstacles to enrollment among diverse populations is needed to improve equity and acceptability in the population genetic screening space.

Chapter 3: Exploring psychosocial impacts, pursuit of follow-up care, and screening reflections among adults receiving positive results in a population genetic screening study

3.1 Abstract

Purpose: In this chapter, we sought to understand the experiences of adults who received positive results through a population genetic screening research study taking place at the UWMC. We focused on psychosocial impacts of results, pursuit of follow-up care, and reflections on this screening strategy.

Methods: Survey data and qualitative interviews were used to assess the psychosocial impacts of receiving results through screening. Survey data was collected both from individuals who were aware of their genetic risk prior to the study and people who learned about risk through screening. Interviews were performed with 14 people who were unaware of their genetic risk prior to screening an average of five months after result return and additionally explored opinions about population screening and resulting plans for follow-up.

Results: Survey data indicated that psychosocial impacts from results were similar between people who were aware of genetic risk prior to screening and those who were not, with harms being limited overall. Overall, interviews echoed these findings, with participants finding results valuable for personal or familial health. Interviewee views of result utility influenced clinical confirmation and follow-up care decision-making. The non-diagnostic nature of screening was considered an important feature to highlight in pre-screening processes. Interviewees also voiced desires to improve and streamline the process of pursuing follow-up.

Conclusion: Psychosocial impacts from genetic screening results were limited. Many potential barriers were present when moving from result return to clinical confirmation to engaging in

prevention. Future programs would benefit from providing support not just during the initial screening process, but later in prevention stages.

3.2 Introduction

An estimated 1% to 2% of the population carries a pathogenic variant that increases risk for preventable conditions such as hereditary cancers or hypercholesterolemia.[30] A population screening approach has been proposed to identify individuals carrying risk variants for these adult-onset conditions who would benefit from medically recommended prevention strategies, but who are often missed under current screening guidelines.[9,34]

To test the feasibility of population genetic screening, members of this dissertation committee designed and led a population genetic screening research study at the UWMC. Details concerning this study are described in Chapter 2. Briefly, individuals who had received care at the UWMC were approached for genetic screening of several genes associated with diseases or disorders of cancer and high lipids, for which medical interventions are available for disease prevention or management. Before testing, participants received written information about the risks and benefits of genetic screening but did not receive traditional genetic counseling. After testing, participants with positive results for a risk variant were contacted by a study genetic counselor for return of results and discussion about next steps. Participants with uninformative results received a results letter online and were given the option to contact study staff in case of questions.

Previous studies in traditional clinical genetic testing settings and among individuals with a family history of cancer indicate that although knowledge of positive carrier status can lead to worry and stress, few patients regret their decision to get tested.[48,49] However, it is possible that individuals who receive genetic testing because of a family history of cancer may respond to

results differently than individuals without a family history who participate in population-based screening. Therefore, it is important to understand the psychosocial impacts of receiving results through screening to minimize the likelihood of harm.

In addition, past research has also found low compliance with recommended medical screenings (e.g., mammograms) and limited uptake of prophylactic surgery among individuals carrying *BRCA1/2* pathogenic variants because of insurance coverage issues and other financial constraints.[25,50] In the context of population screening, learning how people move from receiving genetic results to prevention will provide insight into if these issues persist and what measures should be taken to promote more successful adoption of preventive care.

In this chapter, we used a mixed methods approach to understand the experiences of people who receive positive results through population screening, including psychosocial impacts, plans for follow-up, and reflections on this screening strategy. We analyzed survey data gathered from the screening study at the UWMC to get a broad sense of psychosocial impacts among participants screening positive. We additionally conducted interviews to further explore the psychosocial impacts of screening results and gather information about pursuit of follow-up care. By using both these methodologies, we sought to confirm or elucidate potential contradictions in our findings and understand context around participant experiences with screening and subsequent care.

3.3 Methods

Participants

This analysis included people who enrolled in the population genetic screening study conducted at the UWMC and received positive screening results. These participants included

both individuals who already knew about their carrier status prior to screening enrollment and individuals learning of their genetic risk variant for the first time through screening. The protocol for the population genetic screening study has been described in Chapter 2.

Quantitative Data Collection

As part of the population genetic screening research study at the UWMC, all enrollees were asked to complete 3 optional online surveys at different times during the screening study: before DNA kit request (T0), after DNA kit return (T1), and after receipt of results (T2). Due to the Covid-19 pandemic and changes in staff supporting the screening study at the UWMC, time between these surveys was variable. The average time between the administration of the T0 and T1 survey was 3 months but ranged from 1 to 14 months. The average time between the administration of the T1 and T2 survey was 4 months but ranged from 1 to 18 months. All surveys were sent on behalf of the screening study by the study coordinator via REDCap automated emails. For each survey, a maximum of two reminder emails were sent at one-week intervals following the original send date to encourage completion.

The T0 and T1 surveys contained questions related to participant demographics and health history. Both the T0 and T1 survey assessed personal and family history of cancer and heart attacks. Given higher response rate for the T0 survey, these responses were used in subsequent analysis to maximize available data. The T2 survey contained questions about the psychosocial impacts of receiving genetic risk results through screening using the FACToR (Feelings About GenomiC Testing Results) instrument[51] and the Psychosocial Aspects of Hereditary Cancer questionnaire (PAHC).[52]

Measures

The FACToR (Feelings About GenomiC Testing Results) instrument contains items related to 4 subscales measuring distress/negative emotions, positive experiences/feelings, uncertainty, and privacy concerns (Table 3.1).[51] It has been preliminarily validated and was developed to measure the psychosocial impact of returning genetic results to individuals in research or clinical settings.[51] For each FACToR item, participants were asked to select one of the following choices: not at all, a little, somewhat, a good deal, a great deal, which were scored using a scale ranging from 0 ("not at all") to 4 ("a great deal").

Table 3.1: Survey questions from FACToR instrument

Negative emotions
How *upset* did you feel about your genetic test result?
How *anxious* or *nervous* did you feel about your genetic test result?
How *sad* did you feel about your genetic test result?
Positive feeling
How *happy* did you feel about your genetic test result?
How *relieved* did you feel about your genetic test result?
How much did you feel that you *clearly understood* your choices for disease prevention or early detection?
How *helpful* was the information you received from your genetic test result in *planning for the future*?
Uncertainty
How *frustrated* did you feel that there are no definite disease prevention guidelines for you?
How *uncertain* did you feel about what your genetic test result means for you?
How *uncertain* did you feel about what your genetic test result means for your *child(ren) and/or family's* risk of disease?
Privacy concerns
How *concerned* did you feel that your genetic test result would affect your *health insurance status*?
How *concerned* did you feel that your genetic test result would affect *your employment status*?

The PAHC questionnaire is a screening tool to identify psychosocial problems in cancer genetic counseling settings.[52] Our data analysis focused on the hereditary predisposition (5

items) and the family and social environment (6 items) domains of this questionnaire (Table 3.2). The hereditary predisposition domain includes questions related to concerns around future follow-up plans due to genetic results and the family and social environment domain includes questions related to the impact of genetic results on family and social dynamics.[52] The other PAHC domain included in the T2 survey, "Living with cancer", was excluded from this analysis as it was only relevant to individuals who had ever had cancer. For the PAHC items, participants were asked to select one of the following choices: not at all, a little, somewhat, a good deal, a great deal, N/A, which were scored using a scale ranging from 1 ("not at all") to 5 ("a great deal").

Table 3.2: Survey questions from PAHC Questionnaire

Hereditary predisposition
Are you worried about the chance of being a carrier of a genetic mutation?
Are you worried about having to choose whether or not to go for genetic counseling and testing?
Are you worried about the choice of possible preventative options (screening or surgery)?
Are you worried about coping with the (future) DNA test results?
Are you worried about (fulfilling) your plans for having children?
Family and social environment
Do you feel misunderstood by your partner/family/social circle with respect to genetic testing?
Are you bothered by the lack of support about genetic testing from your partner/family/social circle?
Are you worried about your immediate family's functionality because of genetic testing?
Are you worried about contacting family members about genetic testing?
Are you worried about coping with cancer within the family?
Are you burdened by feelings of responsibility towards family members related to genetic testing?

Quantitative Data Analysis

We calculated descriptive statistics concerning responses to the FACToR instrument and PAHC items for two groups: participants who were previously aware of their genetic risk and participants who learned about their risk for the first time through screening. We stratified

analysis using these groups to disentangle the influence of prior genetic knowledge on psychosocial impacts. We expected individuals learning about genetic risk for the first time through screening to report greater psychosocial harms compared to individuals who already knew about their risk prior to screening, as individuals in the former group may not have been expecting their results, perhaps because of no relevant family history, and likely had less time to become accustomed to them.

For the FACToR instrument, we calculated summary scores for each subscale by summing scores for each item in the relevant subscale. For the positive experiences/feelings subscale, scores were reversed before they were added to ensure that higher scores were indicative of greater psychosocial impact across all subscales.[51] Scores ranged from 0-12 for negative emotions and uncertainty, 0-16 for positive experiences, and 0-8 for privacy concerns. As an exploratory analysis, we conducted a two-sample t-test to assess if FACToR subscale scores were significantly different between the two aforementioned groups at a Bonferroni-adjusted p-value of 0.008.

For the PAHC items, we implemented a cutoff as indication of possible psychosocial problems based on prior use of the questionnaire.[52] For a given domain, if a respondent selected 4 (“a good deal) or 5 (“a great deal) for at least one item, the respondent was classified as positive for psychosocial issues. We reported the percentage of participants positive for psychosocial problems separately for the two previously defined groups: those who were previously aware of their genetic risk and those who learned about their risk for the first time through screening. We used a two-proportions z-test to explore if these percentages were significantly different between the two groups at the Bonferroni-adjusted p-value listed above. All analyses were conducted in R version 4.2.0.

Qualitative Data Collection

Individuals were eligible for interview if they had learned about their risk for the the first time through the population genetic screening research study conducted at the UWMC and had agreed to be contacted about future genetic research. T2 survey completion was optional for consideration for interview. In addition, at least 3 months must have passed since individuals had received positive screening results from the screening study. As pursuit of follow-up care was an area of research interest, this wait time was instituted to give individuals time to begin pursuing such care. To promote recollection about the screening process, individuals were no longer eligible for interview if the time since result return exceeded 9 months. Due to dissertation timeline constraints, individuals were also not eligible if they received results after March 2022.

When determining interview candidates, we employed a quota sampling method, which is designed to ensure that a sample represents certain characteristics of interest seen in the population.[53] This method was used to ensure representation from different demographic groups: age (25-40 y, 41-65 y), gender (M/F), race (as identified by the EHR: African American, Asian, Multiracial/Other, Native American, and White), ethnicity (Hispanic/Not Hispanic), and disease risk (hereditary breast and ovarian cancer, Lynch Syndrome, hereditary hypercholesterolemia), where individuals could represent more than one group.

Using emails listed on the EHR, we emailed UWMC screening participants meeting our criteria to request an interview. If no response was received after one week, we sent a maximum of two follow-up emails to inquire about an interview over the course of the following three weeks. We scheduled interview times via email with those who expressed interest.

All interviews were conducted by NR over the phone in English using a semi-structured interview guide (see Appendix). This guide was informed by a literature review and designed to

elicit opinions about population screening and resulting health behaviors and plans. Verbal consent was obtained at the start of each interview and interviews lasted between 20 to 50 minutes. Directly after each interview, NR recorded a summary of ideas and reflections from the interview. All interviews were audio recorded and transcribed. Transcripts were de-identified to ensure confidentiality. Interview data collection was approved by the University of Washington IRB (000012747).

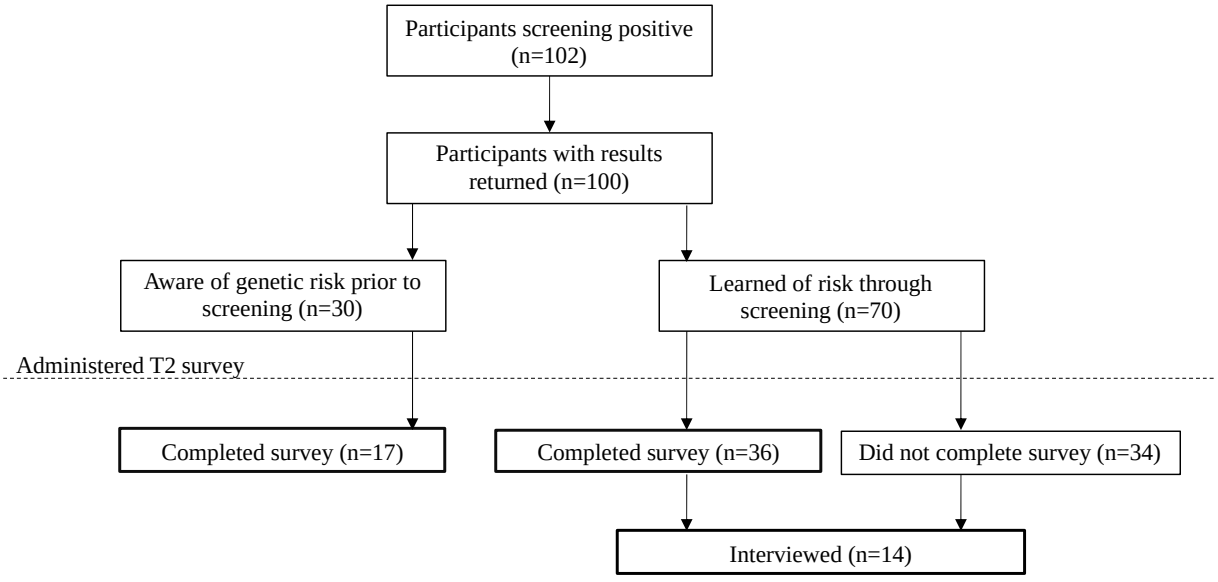
Qualitative Data Analysis

We analyzed interview transcripts in Atlas.ti.8. To develop the codebook, we used a hybrid deductive and inductive content analysis approach.[54] Initial codes were developed based on the interview guide (deductive) and additional codes were developed throughout the analysis process to represent new concepts (inductive). Given our interest in participant reactions to results, experiences with the study, and follow-up care, our codebook primarily focused on these domains. The preliminary codebook was developed by the primary coder (NR) using a subset of 10 interviews. A second coder independently applied this codebook to four interviews. Disagreements in coding were discussed by the two coders and the codebook was revised to ensure definitional clarity, consistency, and to reduce redundancy between codes. The primary coder applied a finalized codebook to all transcripts and the second coder reviewed their analysis. Throughout the coding process, NR kept memos to keep track of coding decisions and emerging themes. To provide a sense of the relative strength of sentiments expressed through the interviews, we calculated counts related to each theme. We also considered the results of our qualitative and quantitative analyses together to get a sense of how results reinforced or disagreed with each other.

3.4 Results

As of June 2022, 102 participants had received positive genetic risk results through the population genetic screening research study taking place at the UWMC. A study genetic counselor was able to reach participants to discuss genetic results in 100 of these cases and confirmed that 30 individuals were already aware of their genetic risk through prior testing. The final sampling frame for survey data analysis included the 100 individuals who were administered the T2 survey after receiving their results (Figure 3.1). The final sampling frame for potential interviewees included 46 individuals who had received positive screening results but were unaware of their risk prior to screening and received these results prior to April 2022 (due to dissertation timeline constraints).

Figure 3.1: Flowchart of individuals included in survey and interview data analysis



Among participants who were already aware of their genetic risk, the average age was 43.5 years old, 87% were female, and 50% had a personal history of cancer (Table 3.3). Among

participants learning about their genetic risk for the first time through screening, the average age was slightly lower at 37 years, 60% were female, and approximately 6% had a personal history of cancer.

Table 3.3: Demographics of participants who received positive screening results from the population genetic screening research study at the UWMC

	All participants	Already aware of genetic risk	Learning of risk for the first time
N	102	30	70
Age[a]	39 [25-60]	43.5 [27-58]	37 [25-59]
Gender[b]			
Female	69 (68)	26 (87)	42 (60)
Male/Other	33 (32)	4 (13)	28 (40)
Prefer not to answer	0 (0)	0 (0)	0 (0)
Race[b]			
African American	9 (9)	3 (10)	6 (9)
Asian	54 (53)	14 (47)	39 (56)
Multiracial/Other	0 (0)	0 (0)	0 (0)
Native American	8 (8)	2 (7)	5 (7)
White	30 (29)	11 (36)	19 (27)
Missing	1 (1)	0 (0)	1 (1)
Ethnicity[b]			
Hispanic	19 (19)	9 (30)	9 (13)
Non-Hispanic	82 (80)	21 (70)	60 (86)
Missing	1 (1)	0 (0)	1 (1)
Personal cancer diagnosis[b]			
Yes	20 (20)	15 (50)	4 (6)
No	82 (80)	15 (50)	66 (94)
Family cancer diagnosis[b,c]			
Yes	66 (65)	28 (93)	36 (51)
No	23 (22)	2 (67)	21 (30)
Don’t know	13 (13)	0 (0)	13 (19)
Personal heart attack[b,d]			
Yes	4 (4)	0 (0)	3 (4)
No	98 (96)	30 (100)	67 (96)

Family heart attack[b,c]			
Yes	41 (40)	15 (50)	24 (34)
No	40 (39)	12 (40)	28 (40)
Don't know	21 (21)	3 (10)	18 (26)
Education[b]			
Less than high school	0 (0)	0 (0)	0 (0)
High school/GED	2 (2)	1 (3)	1 (1)
Some college	12 (12)	5 (17)	7 (10)
College graduate	39 (38)	12 (40)	26 (37)
Advanced degree	29 (28)	7 (23)	22 (32)
Missing	20 (20)	5 (17)	14 (20)
Household Income[b]			
<$50,000	12 (12)	5 (17)	6 (9)
>$50,000 but ≤ 100,000	28 (27)	8 (26)	20 (28)
>$100,000	40 (39)	12 (40)	28 (40)
Prefer not to answer	2 (2)	0 (0)	2 (3)
Missing	20 (20)	5 (17)	14 (20)

[a]Mean [Range]; [b]N (%); [c]Family was defined as a close biological relative (mother, father, son, daughter, aunt, uncle); [d]At any point in time

Survey Results

A total of 50 people completed the FACToR items on the T2 survey (50% response rate), of whom 33 (66%) had learned about their genetic risk for the first time through screening. FACToR scores were relatively similar for both participant groups, with individuals learning about risk for the first time reporting slightly lower positive experiences and slightly more uncertainty compared to individuals who were already aware of their risk (Table 3.4). However, average scores were not significantly different between groups using a Bonferroni adjusted significance level of 0.008. Histograms showing the spread of FACToR scores for both groups are seen in Figure 3.2.

Table 3.4: Average scores for the FACToR subscales

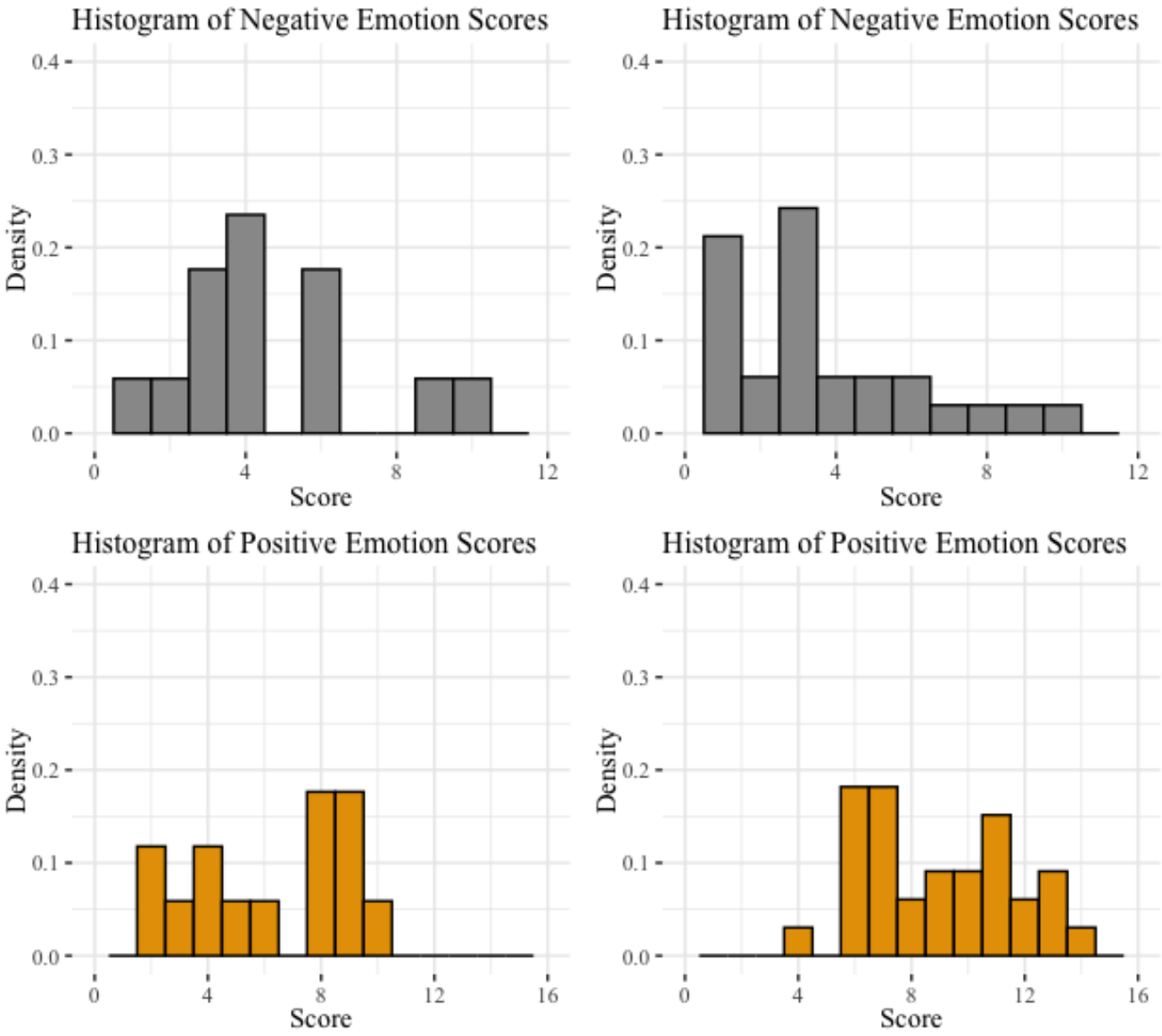
Subscale (Range)	Already aware of genetic risk (n=17)^	Learning of risk for the first time (n=33)^	P-value from t-test
Negative emotions (0-12)	3.8 (2.9)	3.4 (3.1)	0.61
Positive experiences (0-16)	6.1 (4.2)	8.7 (3.1)	0.03
Uncertainty (0-12)	2.5 (3.1)	3.3 (2.9)	0.36
Privacy (0-8)	1.4 (1.6)	1.6 (1.9)	0.75

^Mean (SD); higher numbers indicative of greater psychosocial impact

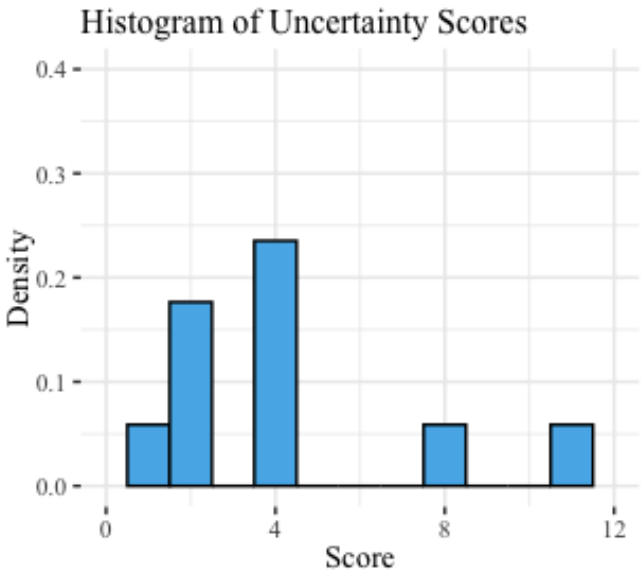
Figure 3.2: Histogram of FACToR scores

A) Among those who already knew about genetic risk (n=17)

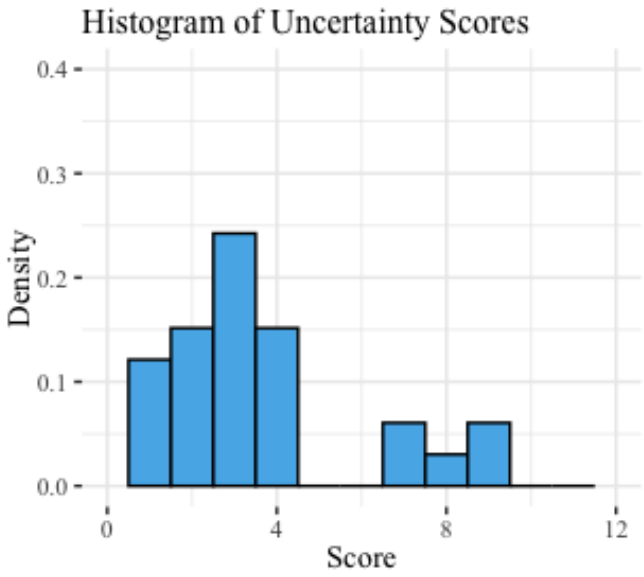
B) Among those who learned about genetic risk through screening (n=33)

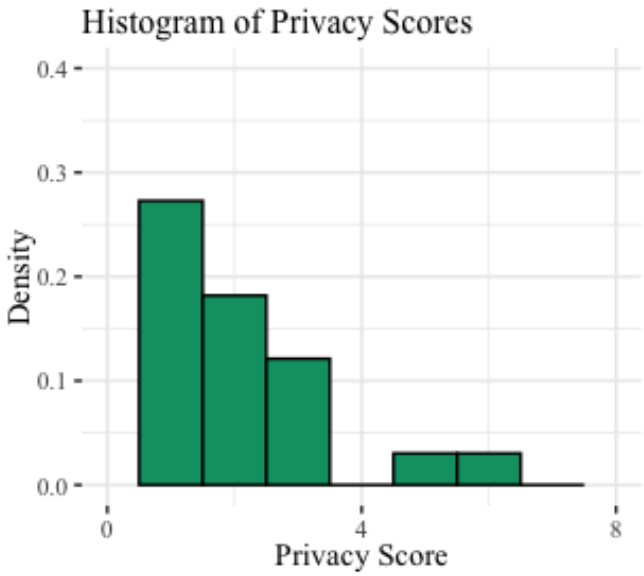


A) Among those who already knew about genetic risk (n=17)



B) Among those who learned about genetic risk through screening (n=33)





Of the 52 people who completed the PAHQ items on the T2 survey (52% response rate), 35 (67%) learned about their genetic risk through the screening study. A lower percentage of respondents learning about their genetic risk for the first time indicated concerns on the hereditary predisposition domain compared to those who were already aware of their risk (Table 3.5), but this difference was not statistically significant at a significance level of 0.008. At this same significance level, concerns related to family and social environment were also not statistically significant. Figures 3.3 and 3.4 show participant responses for these domains.

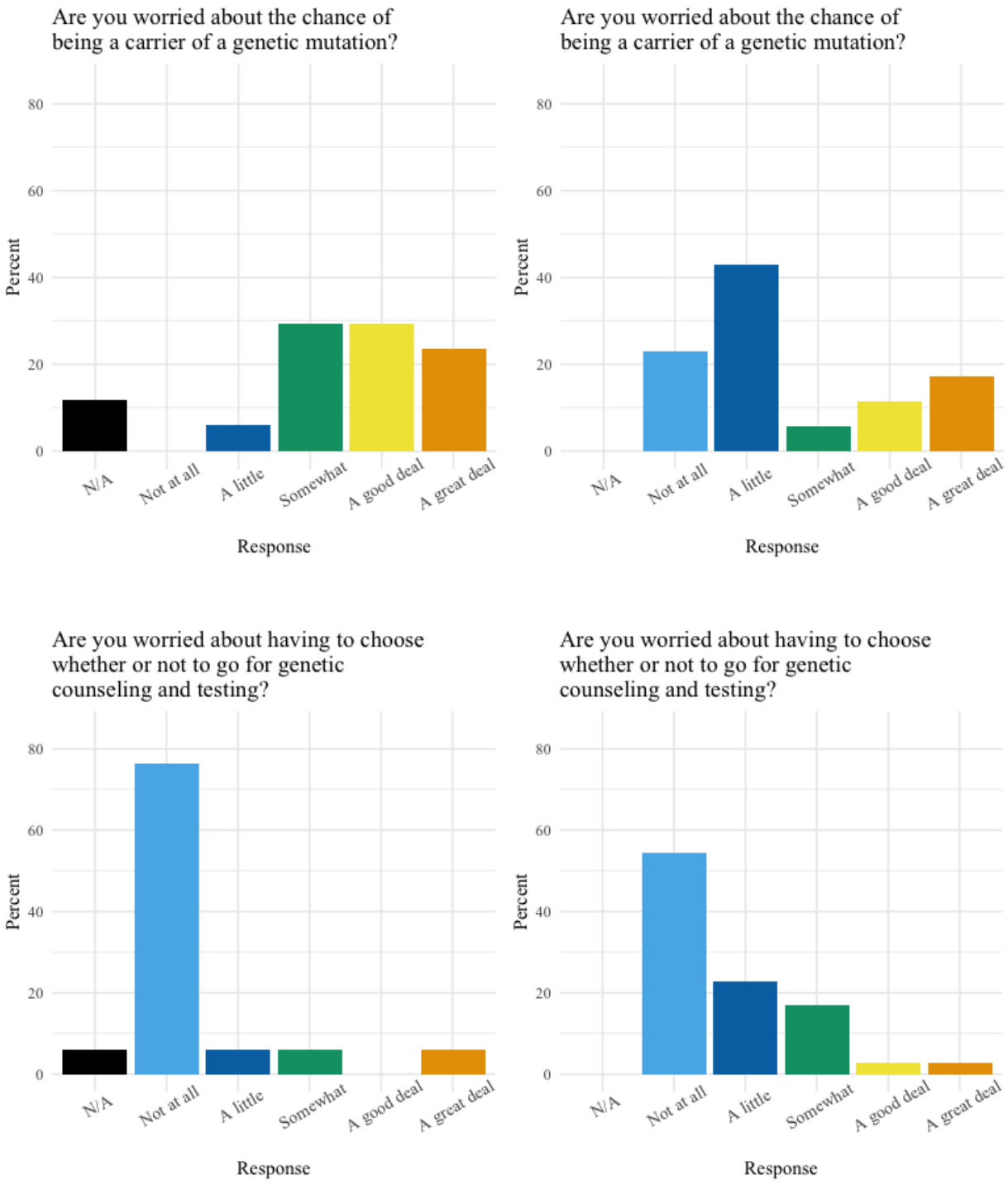
Table 3.5: Percentage of individuals who responded "a good deal" or "a great deal" to at least one PAHC item screening for psychosocial problems

PAHC Domain	Already aware of genetic risk (n=17)	Learning of risk for the first time (n=35)	P-value from z-test
Hereditary Predisposition	58.8	34.3	0.17
Family & Social Environment	29.4	25.7	0.99

Figure 3.3: PAHQ hereditary predisposition responses

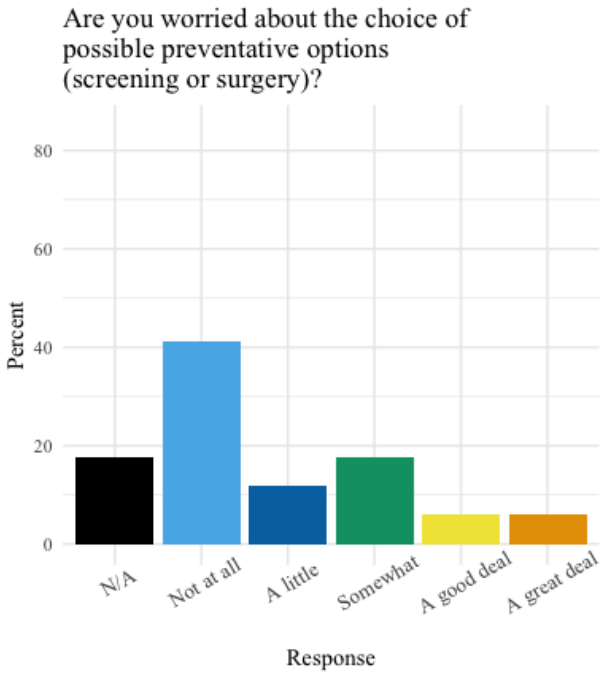
A) Among those who already knew about genetic risk (n=17)

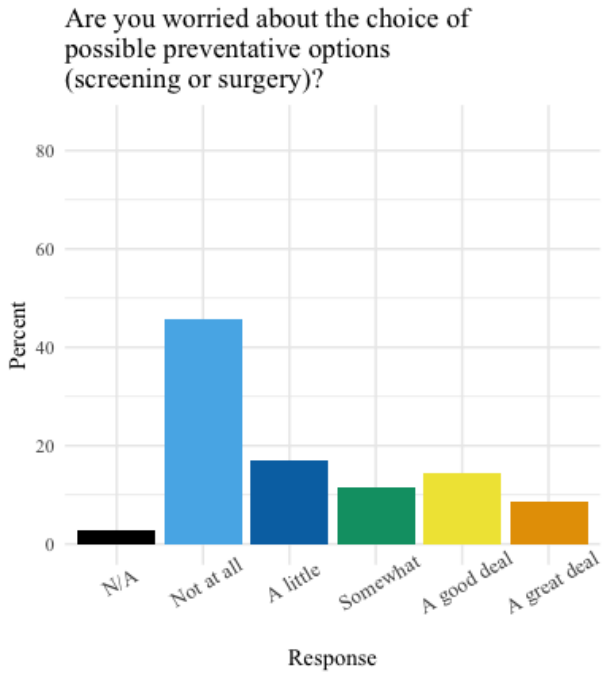
B) Among those who learned about genetic risk through screening (n=35)

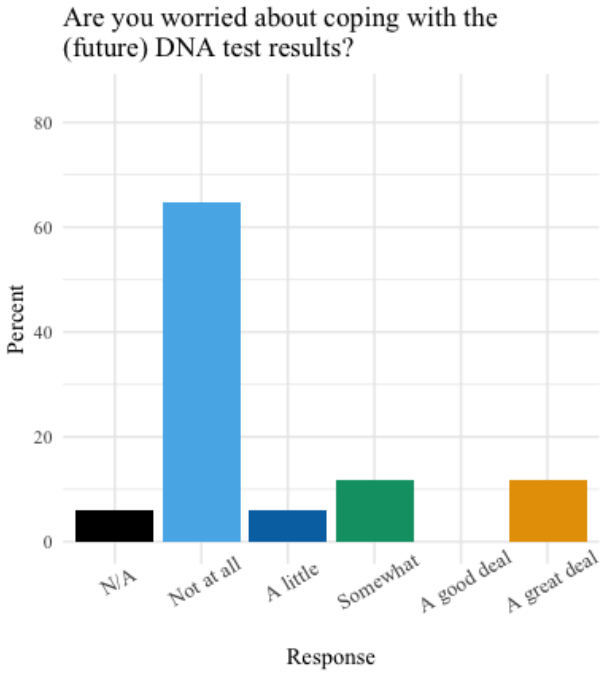


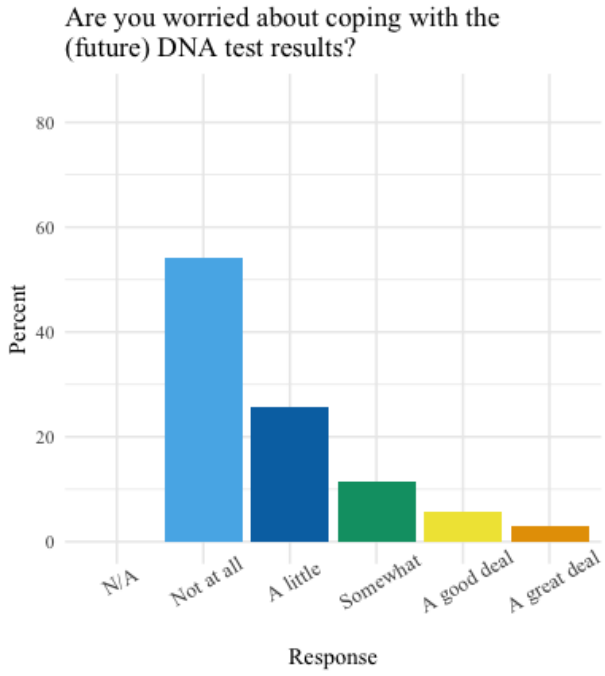
A) Among those who already knew about genetic risk (n=17)

B) Among those who learned about genetic risk through screening (n=35)

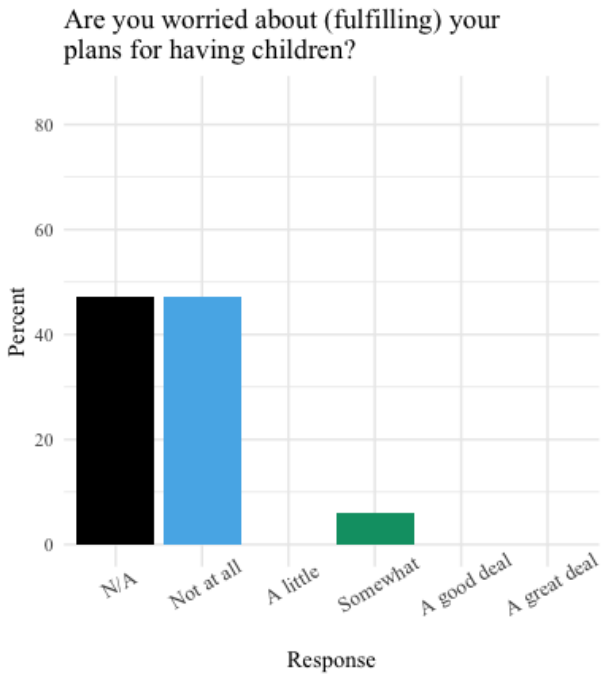








A) Among those who already knew about genetic risk (n=17)



B) Among those who learned about genetic risk through screening (n=35)

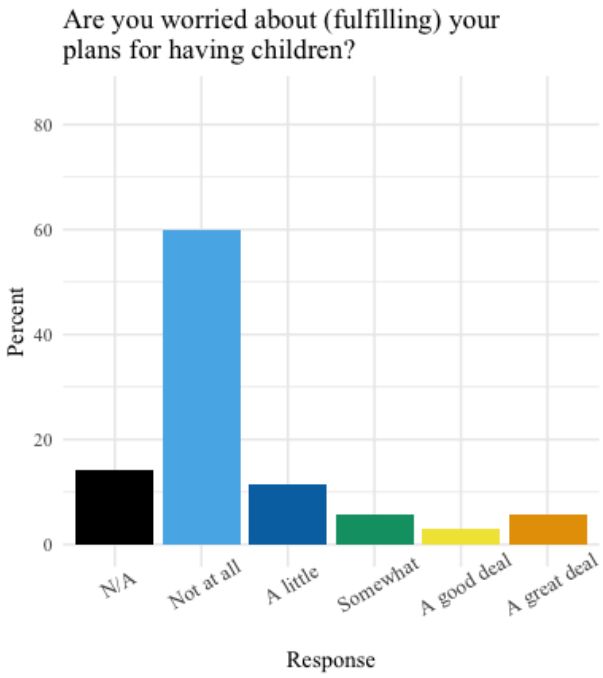
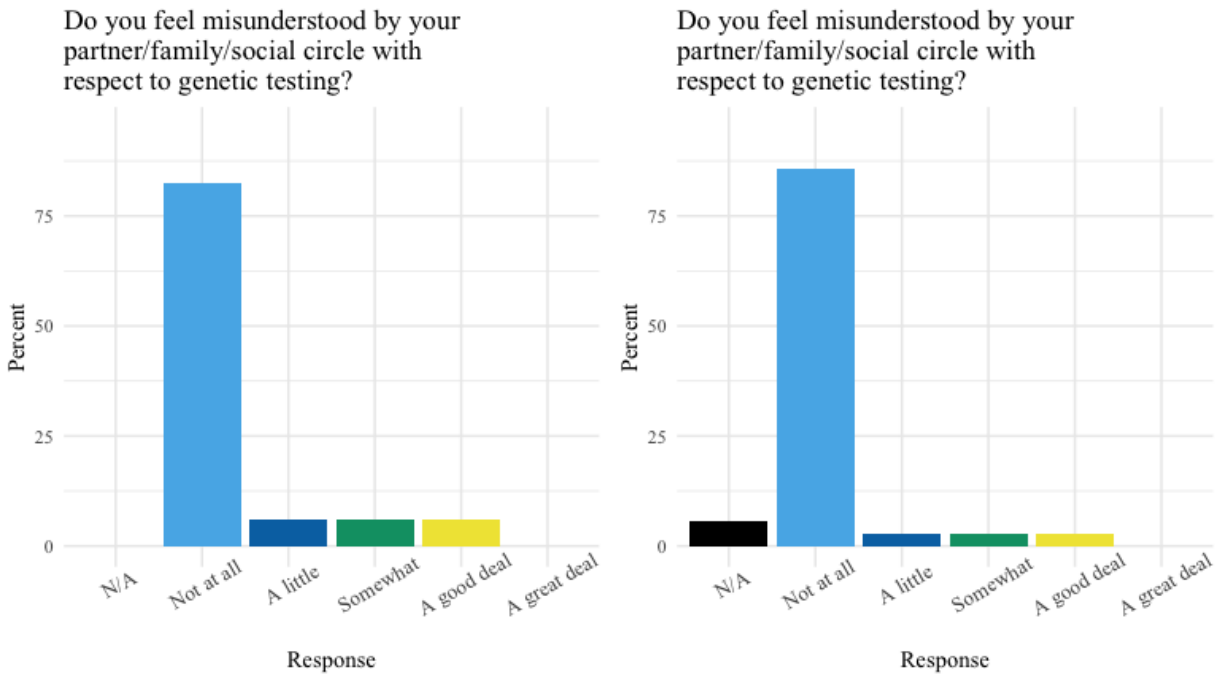
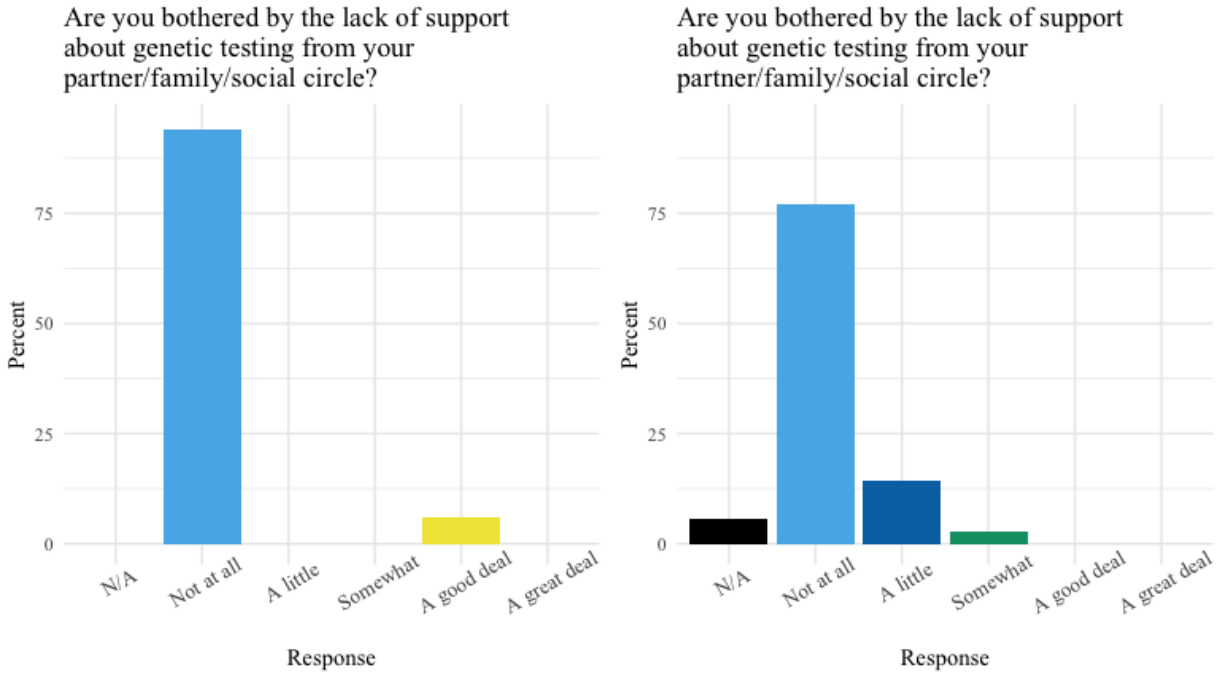


Figure 3.4: PAHQ family and social environment responses

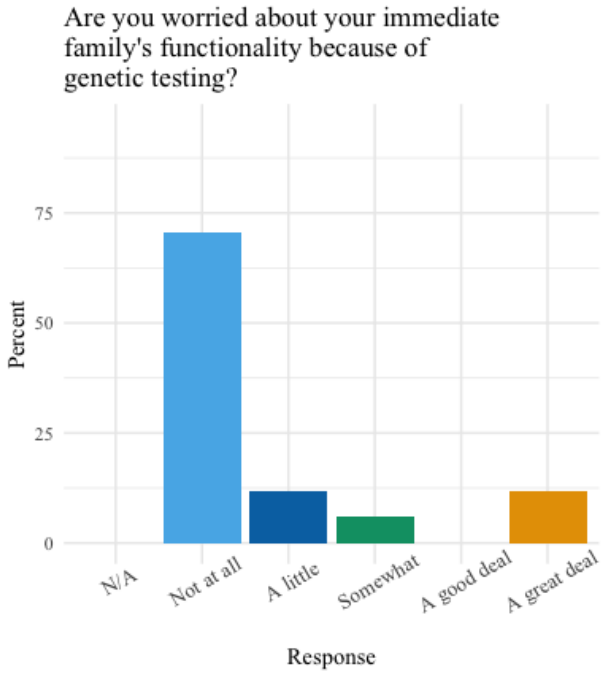
A) Among those who already knew about genetic risk (n=17)

B) Among those who learned about genetic risk through screening (n=35)

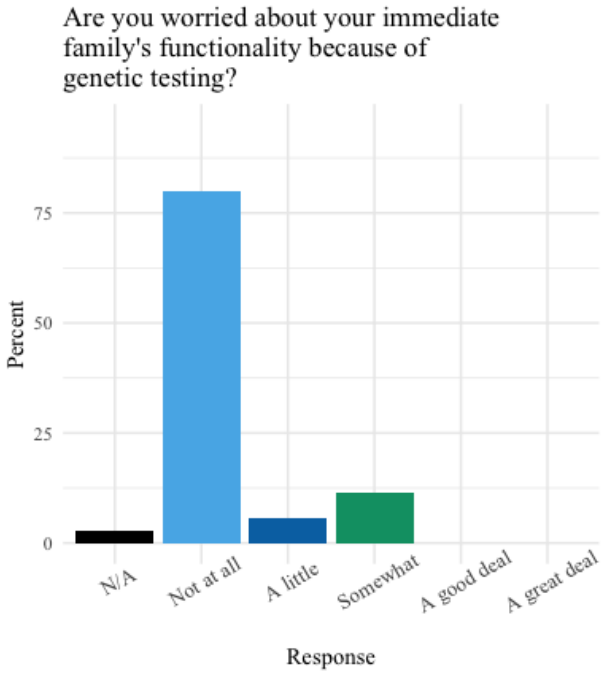


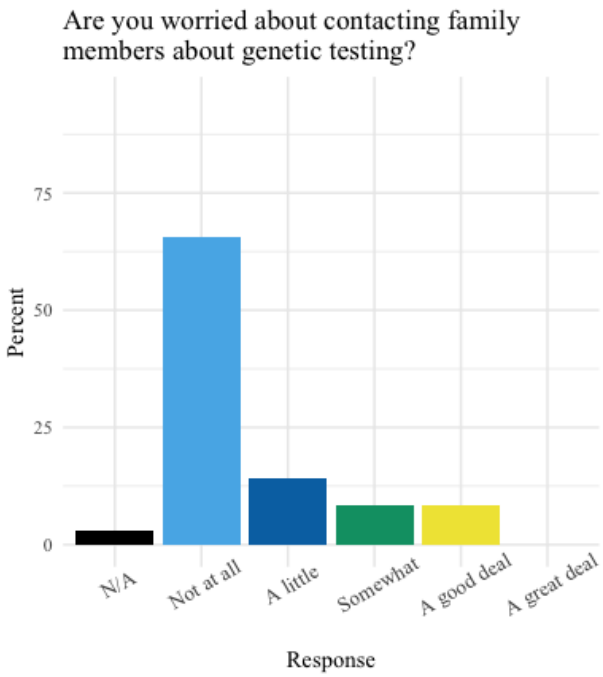


A) Among those who already knew about genetic risk (n=17)

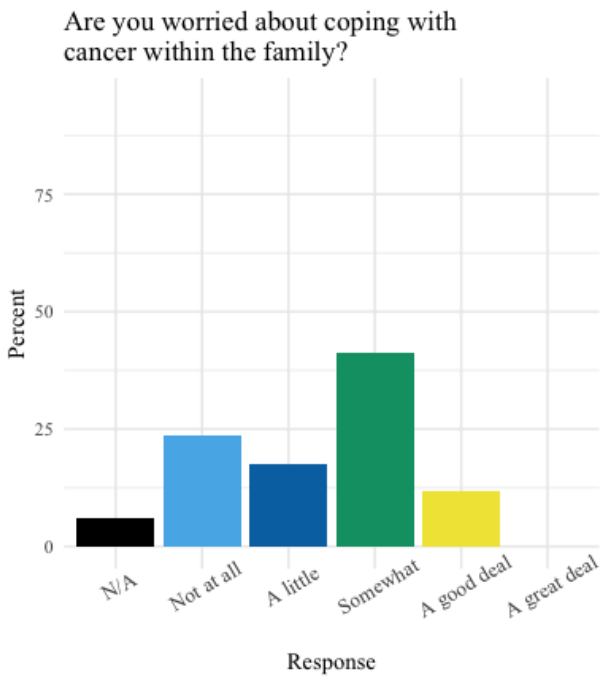


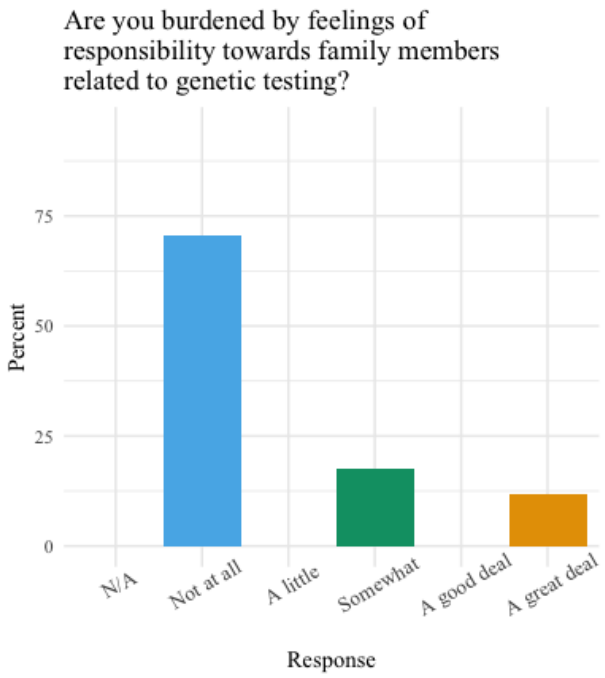
B) Among those who learned about genetic risk through screening (n=35)



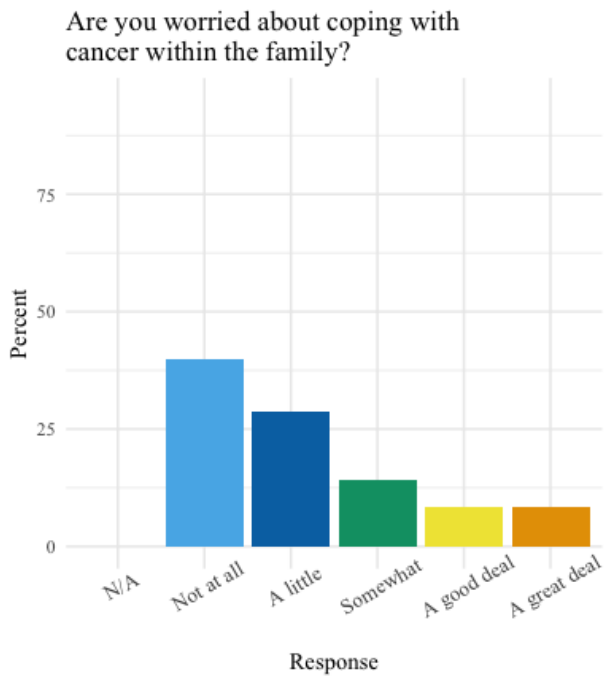


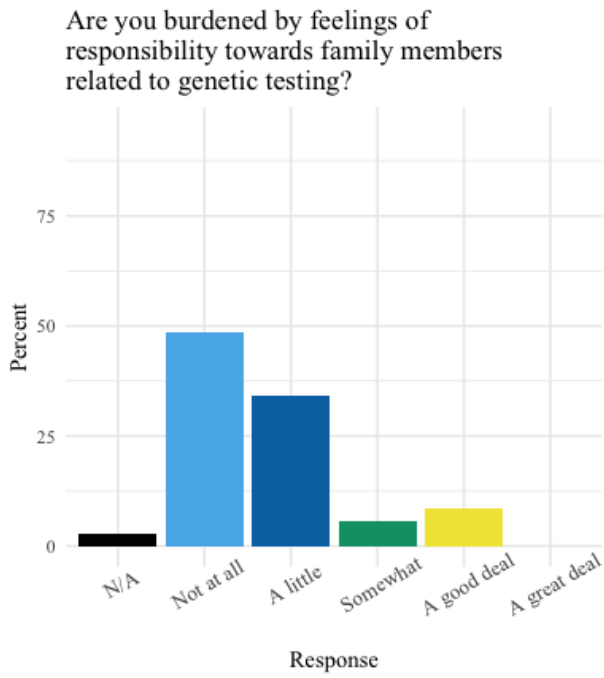
A) Among those who already knew about genetic risk (n=17)





B) Among those who learned about genetic risk through screening (n=35)





Interview Results

Among participants learning about their genetic risk for the first time, 45 were invited for interview. Twenty-four did not respond and 4 declined participation. One of the decliners was unable to participate due to health treatments and another noted time constraints. The remaining 2 decliners provided no reasons for declining. While 17 individuals agreed to interview, scheduling difficulties prevented 3 from occurring. In total, 14 (31%) of the invited individuals were interviewed. Interviews occurred an average of five months after results were returned.

The average age of interviewees was similar to the average age of all participants without prior knowledge of genetic risk from which they were sampled. Racial and ethnic representation closely mirrored the original population as well, but with slightly higher Native American participation and slightly lower Hispanic participation (as indicated by participant EHRs). Interview participants were also more likely to be Female (71%). T1 survey data showed that 13 (93%) were college graduates or had received advanced degrees, and 11 (79%) had a household income of more than $100,000. Two interview participants had a personal history of cancer diagnosis, while another two were aware of a family history of cancer. Overall, participants were largely glad to have participated in the screening program (13/14), finding the information valuable for their own care or for family members. Reflections about psychosocial impacts from genetic results, participant experiences with follow-up care, and screening processes are detailed in subsequent themes.

Understanding and coming to terms with risk information

Participants expressed a range of emotional responses about learning of their genetic risk. For some, there appeared to be very little emotional reaction upon receiving results, viewing results only as information to be incorporated into their life.

> "So I didn't feel sad because it was positive, it didn't make me feel like anything, because it was only just enough information that I needed to take good care of myself." – *P1, Female, 46*

> "It's like your genes are your genes. You can't really do much about them, they're inherited and it kind of is what it is, kind of thing. So regardless of the results it was like, there wasn't really much I could have done in the past to make the results any different. I didn't feel any pressure there that it was like my fault or fear or anything. But the one thing that I did think about was like, oh, I need to let my brother know" – *P6, Female, 32*

As many participants did not have a relevant family history, there were also descriptions of initial feelings of shock as well as an increased awareness.

> "The initial response was a very light level of jarring, right? It wasn't huge, so I didn't feel my life was turned upside down in any sort of way, but I was like, 'Oh, this is something to be aware of. Oh, maybe I should think about what this means for my medical screening, trying to be more proactive in the future.'" – *P4, Female, 32*

Others reflected that learning their genetic result had initially caused concerns and stress, but that eventually these feelings subsided after coming to terms with the information, learning about prevention possibilities and taking steps to monitor their own health status.

> "I was first relieved because it wasn't the worst result. Then I was a little bit concerned, like, 'Maybe I should go see a doctor immediately. Maybe I need to schedule an appointment.' Then [the study genetic counselor] telling me that I needed to do a follow-up thing made me feel like, 'Okay, well, it's not really a done deal,' kind of thing. So, I felt a little less, I think, disturbed by it". – *P8, Female, 26*

> "At that time, I have some like medical issue and I was thinking about, oh maybe this could be cancer that I'm losing my body weight. But after that I regain the weight and I visit my doctors and do all the checks and everything is fine. I think there's no more impact on my mental health anymore." – *P2, Female, 27*

Only one participant described more severe emotional impacts from learning about the results and having to manage the prevention recommendations that followed:

> "I mean, it was jarring to get a random phone call and just have someone tell you that your risks of ovarian cancer were increased and immediately the treatment option was like, 'Oh, you should have surgery'" – *P11, Female, 50*

In particular, this participant expressed feeling taken aback by the matter-of-fact way in which providers were recommending surgery and a sense of urgency to move forward with preventive care. Despite this, the participant still noted they were glad to have participated in screening because they could engage in risk-reducing efforts.

Perceived utility and risk influence follow-up decision-making

Of the 14 interviewed participants, 10/14 pursued or were planning to pursue clinical confirmation testing. The primary motivators for receiving confirmation testing were to ensure

that subsequent screening or other prevention would be covered by insurance providers and to guide potential disease treatment in the future.

> "If I wanted to do anything with these results then I would have to get the confirmation screening done, and so there was a little bit of thinking about, or considering whether that was something that I needed or wanted to pursue. And it took me some time to decide that, and I was like, 'Okay. It sounds like there is something there in my genes. It sounds like it would be helpful to get preventative screening in the future.'" – *P4, Female, 32*

> "I wanted it to be sure that it was in my medical record for my oncologist to validate that. Because apparently that finding can be possibly used for future treatments if the cancer does come back with a vengeance. From what I understand, it can play into what treatment options are there." – *P12, Male, 59*

In two cases, participants received genetic results that would not directly impact their care (e.g., women receiving results related to prostate cancer risk). These individuals chose to pursue clinical confirmation of results to facilitate genetic testing for their family members.

> "If I wanted to get any sort of care for anyone in my family, just thinking about my brother, then it would have to be clinically diagnosed by a physician." – *P6, Female, 32*

Among the four participants who were not planning to clinically confirm their genetic results at the time of the interview, three were planning to engage in prevention measures but did not think clinical confirmation was necessary for these processes. For example, one participant was proceeding with an oophorectomy but had been able to begin scheduling surgery using her research result and because of a family history of ovarian cancer. Another participant was planning to receive colonoscopies at an earlier age but did not think the result confirmation was

necessary given that it was unlikely to provide any new information. This question of necessity was echoed by another participant who had received results about hypercholesterolemia risk. Though planning to monitor her cholesterol with her personal provider, she described a lack of urgency when describing other follow-up:

> "So [the study genetic counselor] did mention the lipid clinic at [the University of Washington] to me. I did want to go, but I don't know why, because it's so close to the university, I really have no excuse. But I didn't end up ever making it over there. I just straight-up just didn't have the time, and it just kind of felt like every time I needed to go there, I think I was like, 'Oh, well. Either way, I'm going to watch what I'm eating. So, is it really necessary?'" – *P8, Female, 26*

The final participant with no plans for clinical confirmation reflected that the results would not change her current care. However, she noted that if she were younger, the information might be more useful to her:

> "I could see if I was maybe, I don't know 30 years old or something, and I didn't already get mammograms. But I'm at an age where I already do my preventative breast cancer care." – *P3, Female, 51*

Desire for streamlining and supporting follow-up

Though most interview participants expressed that they were glad to know about their genetic risk results and were planning to pursue preventive measures, some voiced frustrations with the clinical confirmation process after receiving their research result. While some participants were able to receive insurance coverage for clinical confirmation, others were not. A

participant in the latter group described how the frustration of dealing with insurance had overtaken thinking about the genetic result itself:

> "Either way, I don't know where the bills are coming from…I've had to go back and forth with my insurance company now and had to send an appeal in…but it ended up just becoming very frustrating, and I feel like I was dealing more with the insurance company than even worrying about or thinking about my results…Again, in order to find out what? To find out something I already knew." – *P4, Female, 32*

Participants also discussed a desire to streamline the process of clinical confirmation and other preventive follow-up care so that people would be better able to receive the care they needed. One participant described frustrations with scheduling an appointment for confirmation:

> "It was just one woman with a voicemail inbox that was handling all of this. I couldn't do it through MyChart or anything like that. So that was pain point number one. So there was some back and forth through voicemail trying to get ahold of someone to schedule me." – *P6, Female, 32*

To motivate and improve the follow-up process, participants suggested ideas to facilitate scheduling for clinical confirmation or other appointments and spur changes to their follow-up care based on genetic risk.

> "I don't know if there's a way that you guys can…motivate people to go get it checked out…maybe provide appointment times…Click this button, and you can schedule it really quick," or anything like that. Yeah, something like that would be helpful. The fact that I had to call…make an appointment…I was like, 'I'm definitely not going to end up doing that.'" – *P8, Female, 26*

> "You're supposed to change how they do screenings…But it kind of sounded like that wouldn't necessarily happen automatically unless I brought it up. So, just in general, if there was like a more automatic method for that to propagate through the system." – *P7, Male, 36*

Other participants reflected that if genetic results were going to be provided in this manner, more infrastructure was needed to ensure that people were able to speak with providers and receive the care that they needed.

> "But if you have a study like this, you should have providers ready to see the patients…It took me two months to find someone who would even see me to schedule the surgery. And that was only through my connections." – *P11, Female, 50*

Regarding trying to schedule a colonoscopy:

> "If a system was set up in place for people who didn't necessarily have a ride, that would be good, that way you don't go through the whole entire procedure and then still not get tested in the end" – *P10, Male, 43*

Finally, one participant also voiced frustrations when trying to communicate with their own providers about the genetic risk result, suggesting a need for additional support and education for providers who may be incorporating genetic screening results into patient care plans:

> "That's the big thing I'm getting from a lot of doctors is they don't quite know what to do with the info." – *P13, Female, 37*

Satisfaction with pre-screening information

Eleven of the 14 interview participants expressed that they did not need more information prior to screening. However, of these 11, three expressed that emphasizing the non-diagnostic nature of screening would be helpful to decrease anxiety around participating.

> "But I think that having the emphasis on the information beforehand that just because you get a result that's X, Y or Z doesn't necessarily mean [disease]... I think critically emphasizing that would help decrease anxiety from taking the test in the beginning. I think I could have been less anxious about sending it in." – *P8, Female, 26*

Participants who stated more information was not needed also discussed that informational needs after receiving results are different than those prior to screening and that too much information early on could overwhelm people who would eventually receive uninformative genetic results.

> "Because I'm pretty sure a lot of people in the study probably were negative for all of them. And so there was no special need…no need…to give them more anxiety about it." – *P13, Female, 37*

> "You're obviously in a different mindset before you sign up for a study and after you get results. Right?" – *P11, Female, 50*

Of the participants who requested more information, one generally voiced that more information is good but acknowledged that providing a lot of information in this setting could be challenging given varying familiarity with genetics and technology. Another suggested that highlighting prevention could improve recruitment efforts:

> "Because everybody wants to know what they're going to get out of it…like getting better access to preventative care or learning more about healthcare topics or how to take care of themselves to prevent cancer." – *P6, Female, 32*

The remaining participant voiced that if had they known more about what the study was testing for, they may have thought about it differently. This confusion about what was screened for was reflected in the comments of another participant when discussing the study.

> "And I thought you guys did a good job at asking, 'Do you have genetic tendencies toward anything, any disease?' And it felt like to me that if I said I did, that you guys would look for it as well." – *P5, Female, 56*

Though this participant stated they did not think more information was needed prior to screening, they mistakenly believed the genes the study was screening for could be altered based on personal history.

Recommendations for screening depend on person and circumstance

Participants varied on if they would recommend participation in population genetic screening to others. Half of interviewees voiced that they would recommend screening, without any caveats, because of the potential information that could be learned and the implications this could have for future health:

> "I would recommend it because I think it's really important, again, to have thorough information, have the facts, understand what is maybe predispositioned [sic]…given your genetics, the things that you could do to help prevent those type of things happening to you in the future. Preparing yourself mentally, if…something like that would happen. I

think the more that you have time to think about it and try and do everything that you can to help your body, help yourself, then you should do that." – *P9, Female, 35*

However, the remaining six interview participants expressed mixed opinions about recommending screening to others based on a variety of factors including personal beliefs, utility, and resources. Some expressed that screening is a personal and individual choice and so they wouldn't necessarily recommend it to others:

> "I know like I probably wouldn't actively recommend it to a lot of people because I know a lot of people think differently about these things. I mean, just thinking about my family, I know that my other family members have very different decision-making processes than I do." – *P7, Male, 36*

> "I think…that's an individual choice that people should make, but for the most part, I wouldn't see any reason why someone shouldn't." – *P10, Male, 43*

Some were concerned with the emotional impact of screening and stated they would recommend screening only to people who were well informed about the process and had the ability to pursue care based on screening results:

> "I think for folks, if it could be traumatizing for them or if they don't have the resources to get help. I maybe wouldn't recommend it because if they don't have access to the preventative care, then what does it matter if they know they're pre-exposed to this?" – *P6, Female, 32*

> "I think that's the thing about genetic testing is it's easy to sign up to do it because it's so noninvasive but then the results can have such a dramatic effect. Right? I mean, I think

that's what's interesting about your study is it's a really low bar to say yes to test, but the results, you have to manage the results." – *P11, Female, 50*

Finally, the only participant who stated they would not necessarily receive screening again noted that they would only recommend screening if someone was looking for something specific on which to base decision-making.

3.5 Discussion

Results from this research provide useful insights about experiences with population genetic screening for individuals who received positive risk results. Survey data showed that participants who received positive genetic risk information for the first time had similar levels of concern to individuals who received positive screening results but were previously aware of their genetic variant. Interviews gathering more detailed feedback further suggest that the psychosocial impacts of screening among participants of the population genetic screening study at the UWMC were limited, with negative impacts typically subsiding after learning more about implications of genetic risk and pursuing follow-up care. In interviews where more significant impacts were reported, participants still expressed that screening was a good decision and valued the ability to engage in preventive measures. Overall, interviewees were satisfied with their decisions to participate in screening. However, interviews elucidated potential issues regarding pre-screening information and ensuring people can act on genetic risk results.

Similar survey results between participants who differed in prior awareness of carrier status suggests that the anticipated surprise factor from learning about genetic risks when a significant family history is not necessarily present does not lead to a substantial increase in psychosocial harms. Participants in the two groups may not be as dissimilar as expected

however, as interviews illustrated that some participants learning about genetic risk for the first time did in fact have a relevant personal or family history of disease. This underscores that population genetic screening can identify carriers that have previously gone undetected, as seen in prior studies,[11,32,33] and suggests that early population screening programs may attract individuals already looking to receive testing.

Our survey and interview findings are consistent with prior studies that have sought to examine the psychosocial impacts of receiving genetic risk results in a population screening setting.[55-57] Research among biobank participants in Iceland who were screened for a *BRCA2* founder variant, for example, reported that many participants originally expressed anxiety about finding out their carrier status, but eventually viewed the knowledge as empowering.[55] Similar findings of no excessive psychosocial harm were seen in studies of Ashkenazi Jewish individuals residing in Israel who were screened for 3 deleterious founder *BRCA1/2* variants.[56,57] This suggests that concerns about resulting psychosocial issues may be overstated and potential prevention-related benefits may outweigh the emotional burdens from finding out about risk. Population screening participation may also inherently select for those individuals who are less inclined to experience adverse emotional or mental effects upon learning about genetic risk and weed out individuals who do not consider learning genetic risk information beneficial.

Interview reflections indicate that the pre-screening consent processes appropriately met the needs of most participants. However, interviewees also suggested that better highlighting what genes/conditions are being tested and the non-diagnostic nature of screening could improve understanding and ease anxieties in future population screening programs. Participant views that information needs vary before and after screening and that too much information provided prior to screening could lead to increased anxiety supports the idea of "stepwise knowledge."[56] This

construct was introduced by Lieberman et al. after finding that participants in a population genetic screening trial felt that the information needed to make an informed decision prior to participation was not that same as the information needed after learning about positive carrier status.[56] Therefore, condensed written information prior to screening may be adequate. However, an exploration of alternate pre-screening modalities, such as videos, group counseling, or provider offered screening may address gaps in screening understanding shared by some participants in our study.

For some individuals, interview findings also indicate frustrations related to the pursuit of follow-up care despite being only early on in the prevention seeking process. This highlights a greater need to focus on steps after screening so that people receiving positive risk results can more easily act on these results. Screening programs would benefit from streamlining the clinical confirmation process so that individuals are not navigating this process independently. Such strategies have been adopted by other population screening programs. The Alabama Genomic Health Initiative[16] and Geisinger MyCode Community Initiative,[58] for example, both clinically confirm results prior to returning them to screening participants. Alternatively, the Healthy Oregon Project contacts participants who receive a preliminary positive result and requests a second sample for confirmation testing.[59]

Future programs may also benefit from integrating screening into existing services or by involving primary care providers (PCPs) so that participants are better supported when seeking care based on genetic results. This type of integration or involvement could potentially have relieved issues related to appointment scheduling and enabling appropriate changes to medical care experienced by screening study enrollees at the UWMC. An example of provider integration is provided by The University of Vermont's population genetic screening program, which

currently offers genetic screening though PCPs.[19] This implementation strategy may mitigate challenges with changing care, receiving referrals or meeting with appropriate specialists, though people living in areas without specialty clinics or professionals may still face challenges. Additionally, success of this strategy depends on PCP knowledge about genetic screening and it's possible that limited provider education may lead to inappropriate care decisions.

Limitations

There were limitations to our study. The first was a small survey sample. We expect that any population screening program will detect a small number of carriers, so sample size for individuals screening positive is inherently restricted. However, given limited survey response, comparisons regarding psychosocial impact across people aware of their genetic risk prior to screening and those who learned about their genetic risk through screening may have been underpowered. Participants in our study also tended to be highly educated and have higher incomes, so results from this study may not extend to populations with more varied educational backgrounds or lower income status. Since interviews took place anywhere from 3 to 9 months after result return, participants may also have varied in their study recollections and prevention efforts at the time of interview. This limitation was mitigated by asking participants who were interviewed closer to result return what their future health care plans were, rather than focusing only on what follow-up care they had pursued thus far. Finally, individuals who agreed to be interviewed may have been more motivated to participate due to personal research enthusiasm or experiences with the study, and these experiences may differ from those who chose not to be interviewed. Despite this, findings from this research can provide valuable insight for future implementation of population genetic screening programs in the United States.

3.6 Conclusion

Most participants receiving positive genetic results through the population genetic screening research study at the UWMC reported limited psychosocial harms from learning about their genetic risk. Interviewed individuals generally expressed satisfaction with pre-screening information, but also noted that future programs would benefit from emphasizing the genes/conditions being screened and that screening is not indicative of disease status. Many potential barriers exist when moving from result return to clinical confirmation to engaging in prevention. Our results highlight a need to focus more attention on ensuring that people are able to act on genetic risk results by providing support not just during result return but later in the follow-up process and improving the integration of genetic health services into existing models of care. Future research centered on steps after result return, including long term health decisions, behaviors, and outcomes, is necessary to understand if the anticipated benefits from population genetic screening are realized and to improve follow-up processes for screening participants.

Chapter 4: Addressing health equity challenges in population genetic screening

4.1 Abstract

Purpose: Implementation science frameworks with a focus on health equity have emerged to help guide the introduction of new interventions into healthcare and community settings while limiting health disparities. The purpose of this research was to explore the applicability of such frameworks to guide the equitable implementation of population genetic screening programs.

Methods: We searched PubMed and reference lists for relevant frameworks and examples of their use in health settings. We then assessed if and how selected frameworks provide guidance for different stages of population genetic screening: recruitment, sample collection, result return, follow-up care and prevention, and cascade screening. Findings were synthesized into a list of health equity considerations specific to each stage.

Results: We identified 5 implementation frameworks that focus on health equity. Guidance varied by framework type: determinant (explaining what effects implementation outcomes), process (translating research into practice), or evaluation (assessing implementation). Common characteristics included focusing implementation efforts on populations who have historically experienced health inequities and adapting interventions to fit local context. Process models also highlighted the importance of community partnerships.

Conclusion: Current implementation science frameworks that emphasize health equity offer broad recommendations applicable to population genetic screening program implementation. However, gaps still exist in guidance provided for later stages of population genetic screening. To improve the equitable implementation of genetic screening, future programs may benefit from utilizing one or more of these frameworks or by incorporating the health equity considerations and outcomes compiled in this analysis.

4.2 Introduction

Population genetic screening is defined as genetic screening for unselected members of the population, regardless of personal or family history of disease. It has been proposed as a strategy to increase the reach of genetic services and identify more people at risk for preventable conditions.[9,11,32,32] However, such programs may perpetuate or further exacerbate already existing health disparities if the needs of socially vulnerable groups are not considered.[15]

To limit these harmful consequences, health equity must be a central consideration in the design and implementation of population genetic screening programs. Health equity has been defined as everyone having "a fair and just opportunity to be as healthy as possible."[60] Striving for health equity means focusing on the needs of those who are at greatest risk of poor health due to social circumstance.[21] It involves the elimination of health disparities or health differences that are linked to social determinants, such as race, ethnicity, socioeconomic status, gender, age, religion, disability, sexual orientation, gender identity, geographic location, and other characteristics historically connected to exclusion.[21,61]

Equity is a particularly important consideration in genetics as genetic research has historically been conducted with populations of European ancestry.[62] This exclusion of non-European groups has led to less understanding of variants in these populations and prevents the benefits of genetics services from being realized by all people.[17,62] As such, it is extremely important that current and future genetic research and testing programs prioritize inclusion efforts so that results are more broadly representative, and benefits equitably distributed.[17]

Over the past few years, implementation science frameworks with a focus on health equity have emerged to help guide the introduction of new interventions into healthcare and community settings. Implementation science frameworks have been designed to assist with the

translation of research findings into practice.[63] In the genomics community, there has been a call to apply these principles to improve the incorporation of genomic discoveries into healthcare.[63,64] Emerging frameworks that center health equity have the potential to promote this translation and limit health disparities during program implementation.

In this study we sought to identify and describe published implementation science frameworks that explicitly emphasize health equity and assess the applicability of these frameworks to population genetic screening programs. We discuss how health equity implementation frameworks can guide equity considerations at different stages of population genetic screening and gaps in framework guidance. These findings can help promote the more equitable planning, design, and implementation of future population genetic screening programs.

4.3 Methods

Framework identification

We searched for implementation frameworks designed to promote health equity and limit disparities during the implementation of health interventions by searching PubMed using the following keywords: ("health equity" or "health disparities" or "health inequalities") and ("implementation" or "translation") and ("framework" or "model" or "theory"). One author, NR, screened the resulting titles and abstracts. When articles cited potentially relevant frameworks or described a review of implementation frameworks, NR reviewed the reference lists for pertinent publications. Other frameworks previously known to the dissertation committee were also considered. Articles reviewed were restricted to those that had been published between January 2010 to December 2021, as the focus on health equity in implementation science has become more prominent relatively recently.[65]

Inclusion criteria comprised of frameworks that focused on health equity and the implementation of health services, and had been developed for high-resource settings, as these are the most relevant to population genetic screening. Frameworks were excluded if they were specific to a certain health condition or intervention, provided little guidance for intervention implementation or if the article was not available in English. Discussion papers, or those that only described a need for considering health equity during program implementation or provided no explicit framework or model, were excluded.

Data extraction and evaluation

For each of the selected frameworks, the following data was extracted: name, author, year of publication, type, audience, development, and description. Framework type was determined according to Nilsen's categorizations of implementation science theories, models, and frameworks.[66] Briefly, these categories include determinant frameworks, process models, and evaluation frameworks.[66] Determinant frameworks are designed to assist with understanding barriers or facilitators that influence implementation outcomes and can be used to predict or interpret outcomes.[66] Process models are intended to guide the process of translating research into practice. Finally, evaluation frameworks are designed to specify implementation outcomes for evaluation in order to determine implementation success.[66]

Data synthesis

We assessed the applicability of each framework to population genetic screening by evaluating if and how the framework provided guidance for different stages of population genetic screening (Figure 4.1). Briefly, we conceptualized population genetic screening in 5

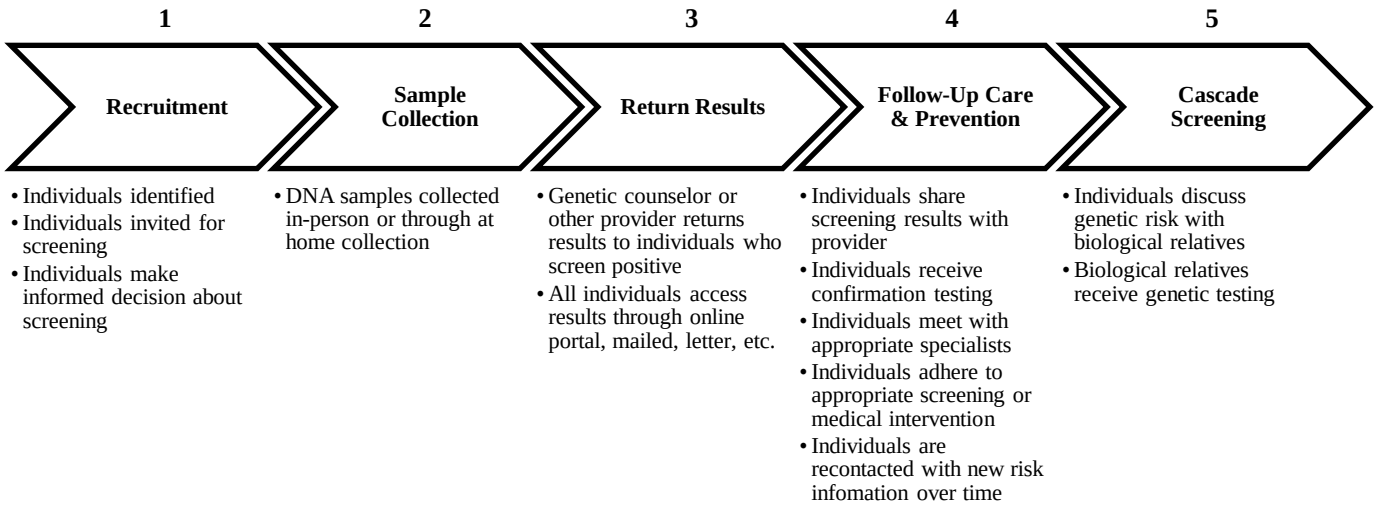
major stages based on the design of pilot screening programs (such as the population genetic screening study at the UWMC) and our understanding of what steps are needed to promote disease prevention. Our descriptive model includes recruitment, sample collection, return of results, follow-up care and prevention, and cascade screening (the notification of biological relatives about genetic risk).

The population genetic screening model presented here is a condensed version of what was given in Chapter 1 (Figure 1.1). For the present analysis, lab testing was not included in the population screening model as this stage is not patient facing. Follow-up care and preventive intervention stages from Figure 1.1 were also combined in this analysis because some screening program designs condense follow-up care procedures, such as clinical confirmation and provider communication, so that these processes occur in prior or later stages of screening. Additionally, many similar framework applications and health equity recommendations were found for both the follow-up care and preventive intervention stages.

To further our understanding of potential framework application, we looked for examples of how each framework may have been used in other settings by examining articles published through December 2021 that cited our selected frameworks. We also searched for evidence of framework validation.

We then compared the selected frameworks and discussed their strengths and weaknesses with respect to guiding the implementation of population genetic screening. Using findings from our applicability assessment, we also compiled a list of health equity considerations and outcomes specific to each stage of population genetic screening.

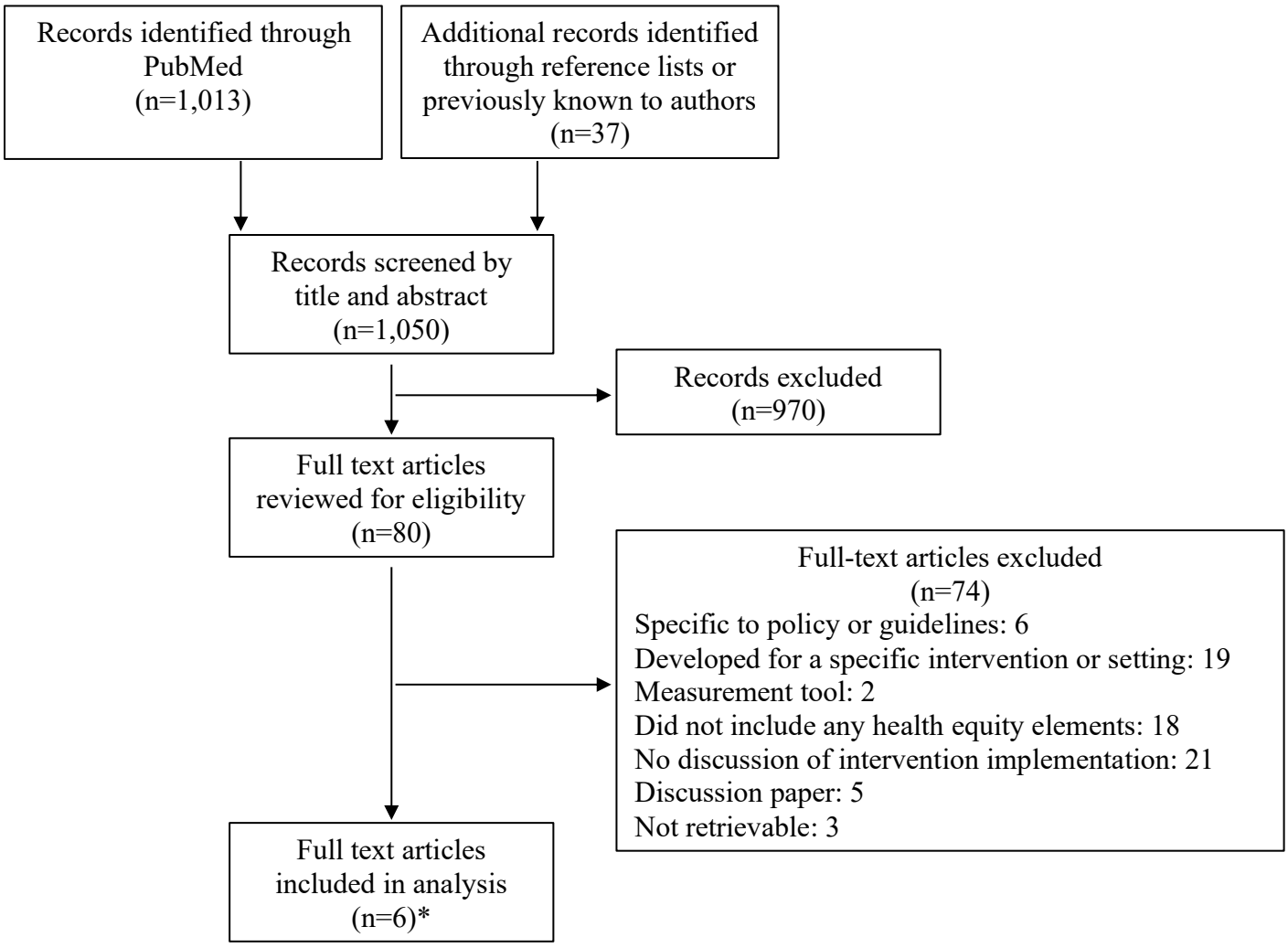
Figure 4.1: Five major stages of population genetic screening



4.4 Results

The initial PubMed search yielded 1,013 results. An additional 37 articles were identified through reference lists or because they were previously known to this dissertation committee. Records were screened by title and abstract followed by a full text review of eligible articles (Figure 4.2). Of the articles that underwent full text review, we excluded frameworks when they were developed for a specific intervention or setting, were not concerned with promoting health equity or reducing health disparities, or provided little guidance for intervention implementation. After review, we identified five frameworks designed to reduce or prevent health disparities during the implementation of health interventions. One framework was described in two of the reviewed articles.

Figure 4.2: Diagram of article search and selection process



*2 articles relevant to the same framework

A brief overview and description of each of the selected frameworks are listed in Table 4.1. Using Nilsen's criteria,[66] the frameworks were categorized as follows: determinant (HEIF[67]), process (Proctor reframed,[68] Transcreation,[69] EquIR[70]), and evaluation (RE-AIM extension[71]). Researchers were the primary intended audience for these frameworks, which were largely conceptually developed, though one (EquIR[70]) was developed using stakeholder engagement.

Our search for evidence of framework validation yielded limited results as, little information was found about if and how any of the five identified frameworks had been validated within the primary articles and in subsequent searches. Framework components/steps are given in Table 4.2. We provide further description of each of the frameworks and an analysis of how they can be applied to the stages of population genetic screening below.

Table 4.1: Characteristics of included models/frameworks

Framework and Author	Type	Audience	Development	Description
Health Equity Implementation Framework (HEIF), Woodward (2019)[67]	Determinant	Researchers	Integration of the implementation science framework, i-PARIHS,[72] and the Health Care Disparities Framework[73]	Framework to assist studying and modifying multilevel implementation and healthcare disparity factors
Reframing implementation science to address inequities in healthcare delivery (Proctor reframed), Baumann (2020)[68]	Process	Researchers	Reframes Proctor et al.'s conceptual model of implementation research,[74] to study healthcare inequities	Framework seeking to address inequities in healthcare by proactively tailoring interventions and implementation strategies to address social determinants of health and explicitly meet the needs of vulnerable communities/settings
Transcreation: an implementation science framework for community-engaged behavioral interventions to reduce health disparities, Nápoles (2018)[69]	Process	Community partners and researchers	Prior methodological frameworks, training resources, authors' experience	Framework for designing and implementing behavioral interventions specifically for communities experiencing health disparities
Conceptual framework of equity-focused implementation research for health programs (EquIR), Eslava-Schmalbach (2019)[70]	Process	Decision makers and researchers	Literature review, stakeholder analysis	Conceptual framework designed to reduce or prevent the increase of existing inequalities during the implementation of programs, policies or health

An Extension of RE-AIM to Enhance Sustainability: Addressing Dynamic Context and Promoting Health Equity Over Time, Shelton (2020)[71]	Evaluation	Not stated	Builds upon the previously developed RE-AIM framework[75,76]	Evaluates public health interventions across reach, efficacy, adoption, implementation, and maintenance domains. Focused on sustainability, with the goal of increasing health impact and health equity over time

Table 4.2: Components of included frameworks

Framework	Components/Steps
HEIF[67]	Factors to understand healthcare disparity determinants: • Clinical encounter: patient-provider interaction • Culturally relevant factors: characteristics unique to a group of people in the implementation effort based on their lived experience • Societal context: physical structures, economies, sociopolitical forces • Context: micro, meso, or macro levels that correspond to inner and outer contexts • Recipients: individuals who influence implementation and those who are affected by its outcomes • Innovation: characteristics of the treatment, intervention, practice, or new "thing" to be implemented • Facilitation: implementation strategies that result in implementation coming to fruition
Proctor reframed[68]	Steps to design intervention and implementation strategies to address healthcare inequities: 1. Focus on reach from the very beginning 2. Design and select interventions for vulnerable populations with implementation in mind 3. Implement what works and develop implementation strategies that can help reduce inequities in care

	4. Develop the science of adaptation 5. Use an equity lens for implementation outcomes
Transcreation[69]	Steps involved in designing, delivering, and evaluating intervention to reduce health disparities: 1. Identify community infrastructure and engage partners 2. Specify theory 3. Identify multiple inputs for new program 4. Design intervention prototype 5. Design study, methods, and measure for community setting 6. Build community capacity for delivery 7. Deliver "transcreated" intervention (e.g., an intervention designed to resonate with the intended community and reduce health disparities) and evaluate implementation processes
EquIR[70]	Cyclical steps to prevent the increase of inequalities during intervention implementation: 1. Identify the health status of the population, including potentially disadvantaged population(s) 2. Identify relevant research questions given the disadvantaged populations, quantify the inequalities to be solved, develop equity-sensitive recommendations for implementation 3. Identify key players and barriers and facilitators for the implementation of equity-sensitive recommendations 4. Design strategies to overcome identified barriers, define monitoring and evaluation strategies, and design the equity-focused communication strategies 5. Monitor implementation outcomes using an equity focus (outcomes listed below) 6. Return to step 1 – Population health status after implementation is the new starting point for further implementation Implementation outcomes to evaluate equity: • Acceptability: perception among key implementation players: health professionals, stakeholders, patients, community, disadvantaged population

	• Adoption: intention, utilization, or action to try to employ the sensitive equity recommendation in the new program or intervention • Appropriateness: relevance or perceived fit, or usefulness or practicability of the program or intervention in the disadvantaged population • Feasibility: extent to which the program or intervention allows to reduce the barriers, and can be carried out in any setting, especially among disadvantaged populations • Fidelity: adherence of disadvantaged population to the equity-focused implementation program or intervention • Implementation cost: Total cost of the program implementation in disadvantaged and non-disadvantaged populations, and the final adjusted cost- effectiveness economic evaluation • Coverage: degree of reach, access, service spread or effective coverage (combining coverage and fidelity) on the disadvantaged population eligible to benefit from the program or the intervention • Sustainability: maintenance, continuation or durability of the program or intervention implemented through short, medium and long- term strategies, including disadvantaged populations
RE-AIM extension[71]	Health equity considerations for evaluation domains: • Reach: Considering social determinants of health (SDOH), who is reached by intervention and who is not? Why? How can reach be improved for populations who are experiencing inequities? • Effectiveness: Are health impacts equitable across all groups based on SDOH? Why or why not? Do certain populations experience higher levels of negative effects? • Adoption: Did all settings adopt the intervention equitably? Which settings staff did/did not and why? Were low-resource settings able to adopt the intervention to the same extent as higher-resource settings? What adaptations will facilitate adoption? • Implementation: Were the intervention and implementation strategies equitably delivered across settings/staff? Which settings/staff were/were not successful in delivery and why? Do all settings/staff have capacity/resources to deliver the intervention on an ongoing basis? What adaptations are needed to promote equity and address SDOH?

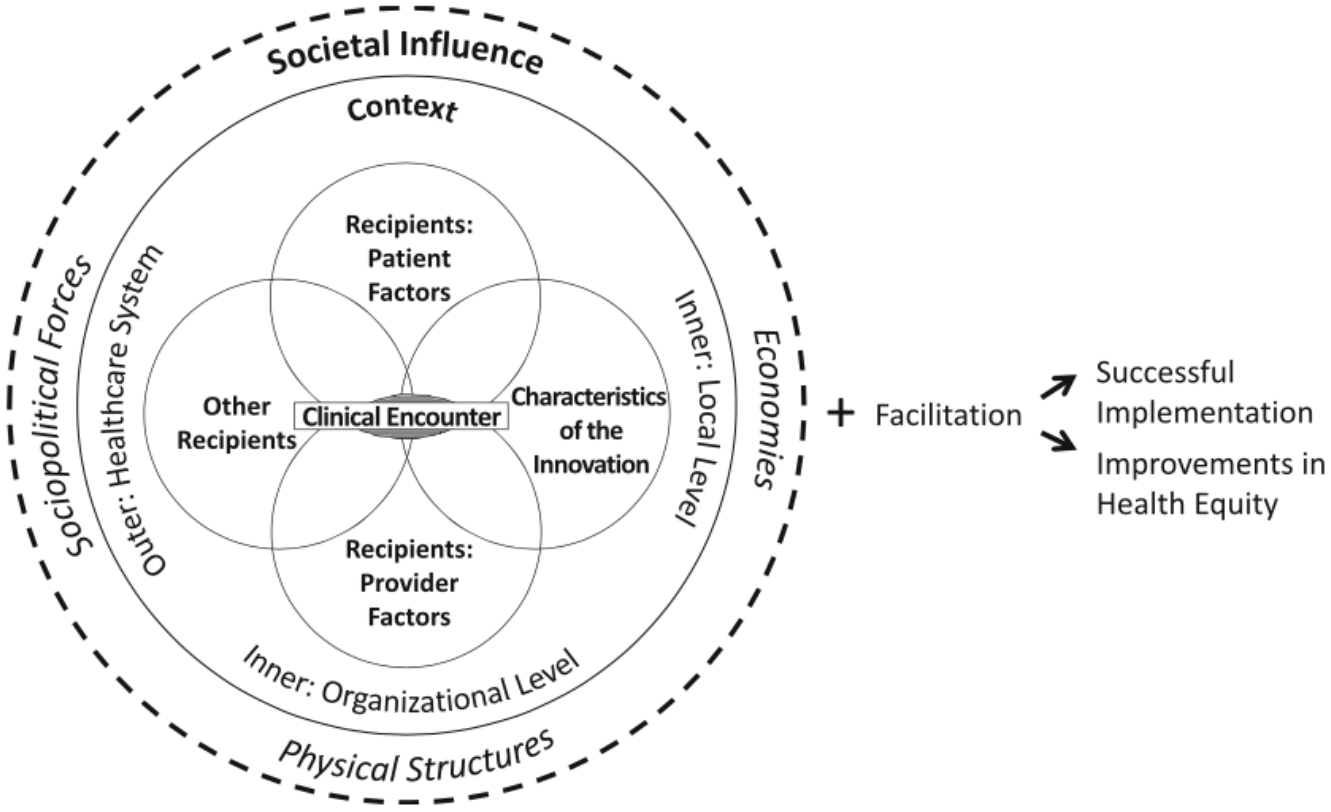
	• Maintenance: Is the intervention being equitably sustained? What settings/populations continue to be reached by the intervention over time? Why? Do intervention adaptations exacerbate inequities over time? Do all settings have capacity to maintain delivery of the intervention? Are sustainability determinants the same across low and high-resource settings? How do SDOH impact inequitable implementation and sustainability?

The Health Equity Implementation Framework (HEIF)

Description

Woodward and colleagues developed HEIF[67] by integrating the i-PARIHS implementation science framework[72] and the Health Care Disparities Framework.[73] This framework (Figure 4.3) is designed to help researchers elucidate factors related to innovation uptake and disparities in healthcare in order to improve outcomes for vulnerable populations.[67] Health equity domains include culturally relevant factors, the clinical encounter and societal context (Table 4.2).[77] Culturally relevant factors are specific to intervention recipients based on their lived experience and can include characteristics such as socioeconomic status, implicit bias, health literacy, trust in providers, language, race and ethnicity.[77] The clinical encounter encompasses interactions between providers and patients, which influence if an intervention is offered by a provider or accepted by a patient.[77] These encounters may be associated with patient satisfaction, trust, and health outcomes and are influenced by inner context at the local (e.g., clinic) and organizational (e.g., hospital) levels, and outer context (e.g., the healthcare system).[77] Finally, the societal context includes economies, physical structures (how environments are built or arranged), and sociopolitical forces (social norms or political forces).[77] These impact health disparities by influencing the inner and outer context, the clinical encounter, and culturally relevant factors.[77] The HEIF has previously been applied to design an interview guide and direct content analysis to identify implementation factors and best practices for social needs screening in primary care settings.[78]

Figure 4.3: Woodward et al. Health Equity Implementation Framework



Application to population genetic screening

The HEIF provides guidance to anticipate possible barriers or facilitators to implementation across all stages of population genetic screening (Table 4.3). For example, during recruitment, attention to cultural factors can help researchers anticipate how health literacy, language, and cultural beliefs influence informed consent and enrollment. As a result, recruitment materials and procedures can be designed to address these areas. During sample collection the physical structures domain of the HEIF can lend insight into how in-person sample collection may facilitate or impede screening for some populations depending on access to reliable transportation and the location of facilities. When results are returned, addressing potential clinical encounter issues, such as if all people with similar results receive appropriate information and have the same access to providers, can also improve equitable treatment. During

the follow-up care and prevention stage, understanding if physical spaces where prevention may occur are accessible to people with disabilities will also highlight potential challenges to equitable care. Finally, in the cascade screening stage, reflecting on sociopolitical forces, such as laws related to genetic privacy, may illuminate barriers to information sharing among biological relatives.

Though the above considerations are by no means exhaustive, they are illustrative of how HEIF health equity domains can be used to systematically anticipate and identify where disparities may or are occurring across all stages of population genetic screening. These domains also offer a means of understanding if implementation barriers may be unique to a specific population group or a barrier across groups. This can assist in the adaptation of population genetic screening procedures by highlighting which barriers are important to address in order to promote more equitable enrollment, retention, and follow-up care.

Proctor reframed

Description

Baumann and Cabassa reframed the Proctor implementation science framework to provide an example of how to apply an existing framework to address inequities in healthcare.[68] The original Proctor framework posits that interventions differ from their implementation strategies and requires the involvement of various stakeholders at multiple levels.[74] The original Proctor also proposes outcomes in three interrelated but distinct domains: implementation (e.g., feasibility, fidelity, acceptance), service (e.g., efficiency, safety, effectiveness), and client (e.g., satisfaction, function).[74] The reframed Proctor framework builds on the original by emphasizing collaborating with stakeholders and community members throughout intervention planning,

design, and implementation in order to understand and meet the needs of historically underserved communities (Table 4.2).[68] It proposes continually adapting programs based on the needs of populations and with the goal of reducing inequities through systematic changes to intervention and implementation strategies.[68] Finally, Proctor reframed suggests conducting descriptive and explanatory studies to identify factors that contribute to inequities in implementation outcomes.[68] We did not identify any published applications of Proctor-reframed in health settings.

Application to population genetic screening

Proctor-reframed specifies guidance relevant to the recruitment stage, including ensuring that populations that have previously experienced inequities in genetic services are included in population genetic screening programs. Suggested strategies for enhancing inclusion are conducting population screening programs in non-traditional settings such as in faith communities or community centers. This framework also discusses how face to face presentations with community members and person to person recruitment can assist with enrolling people who would otherwise not participate.

When considering other population genetic screening stages, Proctor-reframed offers high-level guidance. Common themes that may be pertinent throughout population screening programs include collaborating with stakeholders and community members and examining the acceptability of intervention procedures (Table 4.3). This collaboration can ensure that community social and cultural values are addressed during the development of program materials and processes. For instance, when designing strategies for how results are returned, collaboration with partners can help determine preferred methods of communication, and how much and what type of information may need to be provided.

Finally, the emphasis on implementation outcomes in Proctor-reframed and considering how these may be impacted by social determinants of health provides a quantitative means to understand inequities that may be emerging throughout screening stages and monitor how program changes impact these inequities. Suggestions to continually adapt interventions to fit population needs, though broad, are applicable when thinking about how to sustain population genetic screening programs and ensure that issues during ongoing care or familial communication after result return are addressed.

Transcreation

Description

Transcreation is defined in this framework as the process of planning and delivering interventions to reduce health disparities that resonate with the intended community.[69] Nápoles and colleagues created this framework to address and account for the differences that occur between original intervention implementation settings (often among mainstream populations or in academic settings) and when interventions are adopted among a health disparity population.[69]

Collaboration is a central tenant of Transcreation, which proposes stakeholder and community involvement through the entire process of intervention design, implementation, and adaptation (Table 4.2).[69] This framework assumes the presence of an established partnership between researchers and community members and a shared understanding of the disparity to be addressed.[69] As part of the framework's proposed collaboration, Transcreation suggests involving community workers in the implementation of the intervention by training them in intervention delivery.[69] Fitting interventions to context and population needs is another main principle of Transcreation, which recommends incorporating community knowledge, scientific

evidence, and theories related to behavior change and health disparities throughout the implementation process.[69]

Transcreation has previously been applied in other health settings. For example, it has been used to adapt an intervention designed to improve stress management among cancer survivors to better meet the needs of Latina breast cancer survivors living in rural settings.[79]

Application to population genetic screening

Transcreation provides guidance for the initial recruitment stage of population genetic screening by suggesting focusing attentions on populations who experience disparities in access to and utilization of genetic services (Table 4.3). Through the incorporation of past scientific evidence, programs can also adopt recruitment strategies that have been proven to work in similar settings.

Similar to Proctor reframed, Transcreation offers high level direction and places a large emphasis on community partnerships and collaboration through all phases of program design, implementation, and monitoring.[69] Doing so ensures that population genetic screening procedures reflect community values and preferences. Through this collaboration, screening programs can incorporate content that fits the population of interest's culture, language and learning style. This sensitivity to specific needs of a given population is relevant throughout all stages of population genetic screening, though resource challenges may emerge when a general population screening program involves multiple communities.

The idea of training people in the community to assist with screening can potentially address this challenge and is applicable to all stages of population genetic screening. In particular, community members could be trained to provide cultural, informational and logistical support to specific communities within a general population. During recruitment, this can help

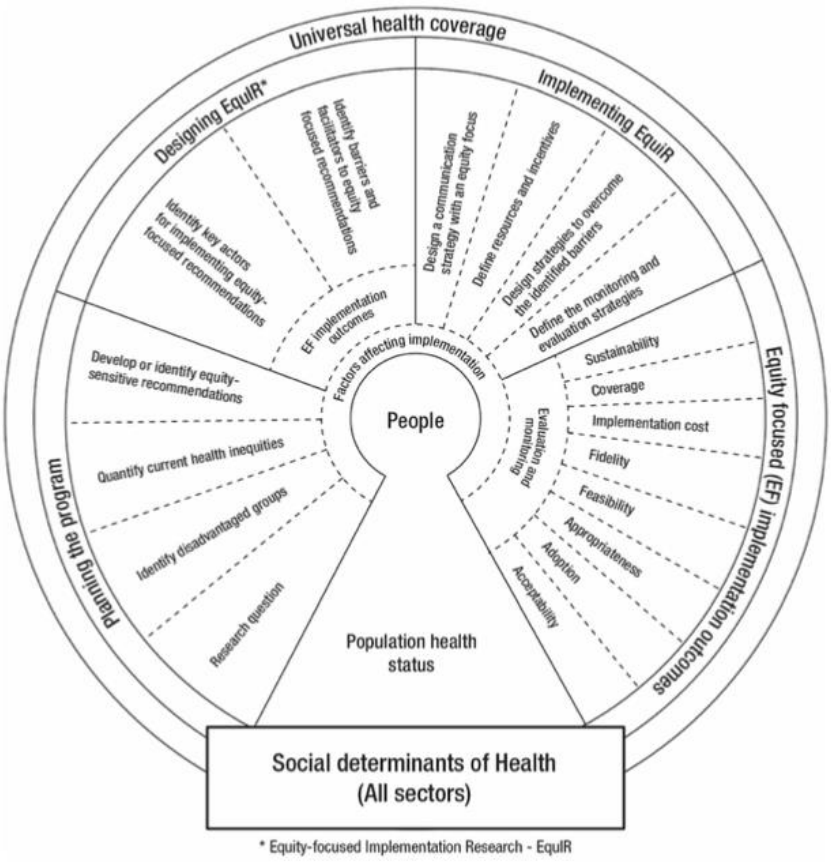
promote informed decision-making around screening. In the follow-up and prevention stage, community members could be trained as patient navigators who assist individuals with information regarding insurance or recommended medical interventions.

EquIR

Description

Eslava-Schmalbach and colleagues developed EquIR for use by researchers and decision makers to reduce or prevent the production of health inequities during the implementation of health programs, policies, or interventions.[70] This conceptual framework (Figure 4.4) is described as a cycle consisting of planning, design, implementation, and evaluation phases, with social determinants of health being considered throughout.[70] The cycle begins with identifying disadvantaged populations and quantifying current health inequalities (Table 4.2).[70] It then suggests developing and implementing recommendations to meet the needs of disadvantaged populations with key players such as health professionals, patients, community members, and stakeholders.[70] It finishes by recommending the monitoring of implementation outcomes (Table 4.2) and identifying how the intervention has impacted the health status of populations receiving the intervention.[70] From here the cycle continues and the new population health status becomes the starting point of the intervention.[70] Beyond its initial development, we identified no examples of the use of EquIR to guide implementation of health-related interventions or programs.

Figure 4.4: Eslava-Schmalbach et al. Conceptual Framework of Equity-focused Implementation Research



Application to population genetic screening

EquIR calls attention to thinking about how standard population genetic screening procedures might lead to the exclusion of disadvantaged populations (Table 4.3). For example, if people are recruited for screening through primary care providers, individuals who do not have regular access to a provider, perhaps due to income, occupation, or other lifestyle characteristics, will not have the option to receive screening. Similarly, if sample collection requires an in-person appointment, this may exclude individuals who do not have the time or ability to come to the clinic or other testing site. While the consideration of how populations may be excluded is broad, this can guide implementation considerations throughout stages of population screening.

With EquIR's proposal of quantifying potential inequities, researchers can also anticipate how population genetic screening programs may exacerbate health disparities. Though another fairly general consideration, this thinking can be applied to any stage of population screening. For example, inequities may occur during return of results if procedures require a mailing address to receive a results letter and some individuals do not have a regular place of residence. Anticipating this barrier can lead to program design that involves flexible return of results procedures where individuals can receive results in a manner that best suits them (e.g., online or mailed letter).

Using the outcomes provided by EquIR, population genetic screening programs can also be evaluated to understand how they impact disadvantaged populations. For example, measures of acceptability and appropriateness can be applied during recruitment, sample collection, and return of results stages to understand stakeholder perceptions of fit and usefulness of program procedures (Table 4.3). Measures of fidelity and coverage may be useful during follow-up care and cascade screening stages for understanding how often people receiving positive screening results are able to act on these results and how often risk information is shared with biological relatives. In addition, the cyclical nature of EquIR promotes ongoing program adjustments informed by these outcome measures.

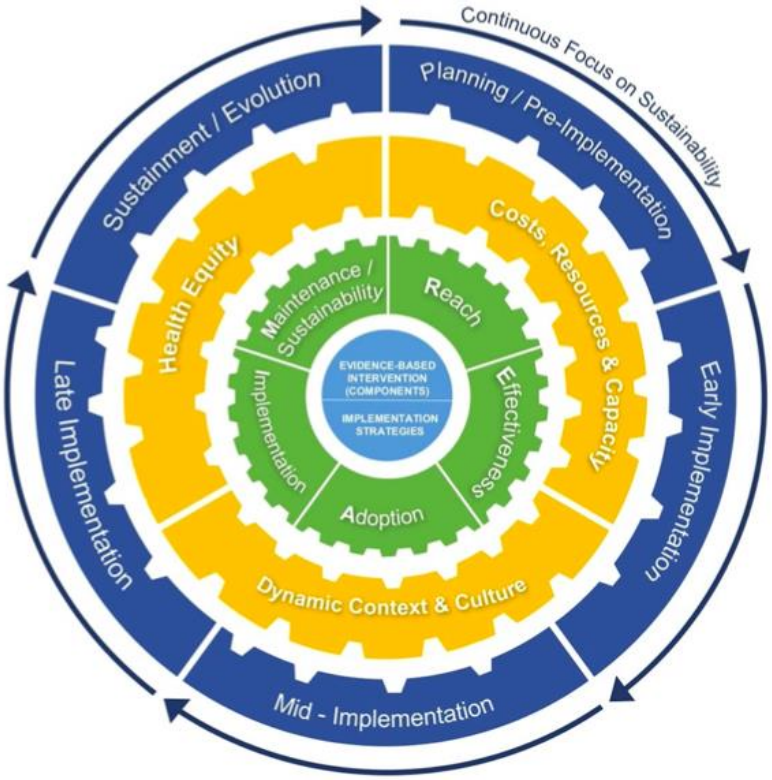
RE-AIM extension

Description

The extension to the RE-AIM framework (Figure 4.5) authored by Shelton and colleagues is designed to promote sustainability and health equity.[71] The original RE-AIM framework focuses on evaluation and includes both individual and staff/setting level domains:

Reach and effectiveness (individual), adoption and implementation (staff/setting), and maintenance (individual and staff/setting).[75,76] While the extension to RE-AIM discusses these same domains and previously described indicators,[75,76] Shelton et al. provide additional guidance to consider health equity during the measurement of these indicators (Table 4.2).[71] This guidance focuses on assessing indicators over time across different populations of focus (defined by age, race, ethnicity, disability, insurance status, literacy level or other social determinants of health), to identify and address health inequities.[71] The extension to RE-AIM also considers the link between health equity and costs or resources and suggests incorporating cost estimates and resource requirements into planning discussions with stakeholders.[71] This framework has previously been used to evaluate the implementation of a COVID-19 vaccine program seeking to facilitate equitable vaccine access and uptake among Latinx community members.[80]

Figure 4.5: Shelton et al. An Extension to RE-AIM



Application to population genetic screening

The outcome indicators and health equity considerations listed by RE-AIM extension give measures that can be monitored at each stage of population genetic screening to assess inequities (Table 4.3). During the recruitment stage, relevant indicators include the number of people who are offered screening and the number of people who agree to screening. Taking into account social determinants of health when interpreting these indicators can determine if all populations are offered and enroll in screening similarly and reveal which populations are not reached. Reach can also be ascertained across social determinants of health during sample collection (number of people who want to participate, number of people who provide samples), return of results (number of people who provide samples, number of people who receive results) and cascade screening (number of people who communicate about risk with relatives) to elucidate inequities that may be emerging during these stages.

Measures of effectiveness are also relevant for the return of results, follow-up care, and cascade screening stages. For return of results, indicators include the number of people experiencing psychosocial harms upon learning results. For follow-up care and prevention, relevant indicators are the number of people who are able to engage in preventive interventions who desire it and the number of people who experience psychosocial harms because of difficulties accessing care. During cascade screening, indicators include the number of biological relatives who receive testing. Similar to assessments of reach, understanding effectiveness indicators across different social determinants of health can reveal if harms are experienced more by certain groups compared to others and if some groups have less access to preventive services.

Finally, RE-AIM indicators of maintenance can be used to measure inequities in follow-up care and cascade screening stages over time by tracking who is adhering to preventive

interventions or engaging in familial risk communication. However, this type of tracking is likely resource intensive as it will involve engaging with screening participants long after they initially receive genetic screening.

Table 4.3: Applicability of frameworks to population genetic screening programs

Framework/Population Screening Stages	Recruitment	Sample Collection	Return Results	Follow-Up Care & Prevention	Cascade Screening
HEIF[67]	Anticipate and identify barriers and facilitators using health equity domains: culturally relevant factors, the clinical encounter and societal context				
Proctor reframed[68]	Include populations experiencing inequities. Conduct programs in non-traditional settings.				
	Collaborate with stakeholders and community members				
	Assess acceptability and adapt interventions				
Transcreation[69]	Focus on populations experiencing inequities. Adopt recruitment strategies that have worked in similar settings.				
	Stakeholder and community participation				
	Involve and train community health workers				
EquIR[70]	Consider how programs and procedures may exclude disadvantaged communities				
	Quantify potential inequities				
	Develop recommendations to address inequities				
	Relevant outcomes: acceptability,	Relevant outcomes: acceptability, appropriateness,	Relevant outcomes: acceptability, appropriateness, coverage, fidelity	Relevant outcomes: coverage, fidelity	Relevant outcomes: acceptability, coverage, fidelity

	appropriateness, coverage	coverage, fidelity			
RE-AIM extension[71]	# offered screening, # who enroll	# who want to receive screening, # who provide samples	# who have results available, # who receive results, # who experience psychosocial harms from results	# who engage in preventive interventions who desire it, # who experience psychosocial harms because of difficulties accessing care (measure over time)	# who communicate about risk with relatives, # of biological relatives who receive testing (measure over time)

4.5 Discussion

In this chapter we outline relevant equity considerations for population genetic screening program implementation guided by five selected frameworks: HEIF,[67] Proctor reframed,[68] Transcreation,[69] EquIR,[70] and RE-AIM extension.[71] Results from this analysis depicted in Table 4.3 indicate stage-specific recommendations (or lack thereof) and guidance applicable across stages. These results may offer insights for researchers designing new population genetic screening programs and assist with identification and selection of relevant frameworks to direct implementation.

There are a number of shared characteristics for promoting health equity consistent across the analyzed frameworks. The first was to focus implementation efforts on populations who have historically experienced health inequities. This is a crucial consideration as placing specific emphasis on vulnerable populations at the beginning of implementation planning can reorient implementation design and procedures to better prioritize the needs of such communities. Another common element across frameworks was to adapt interventions to fit local context and meet the needs of vulnerable communities. Doing so can limit the implementation gap, which occurs when the context where interventions are designed and developed does not align with realities of implementation settings. Constraining this gap can increase the appropriateness of an intervention.[68]

The identified frameworks were conceptually focused, rather than validated theories, and the guidance provided varied by framework type, as expected. As such, different frameworks may be better suited for different times during implementation. The process models, Proctor reframed,[68] Transcreation,[69] and EquIR,[70] for example, tended to be high-level, and provided overarching considerations and recommendations for program design, implementation, and

evaluation rather than specific guidance that lends itself to individual stages of an intervention like population genetic screening. Regarding screening, Proctor reframed[68] and Transcreation[69] recommendations applied most directly to the recruitment stage. While all three process models described evaluating implementation outcomes keeping social determinants and differences in outcomes across populations in mind, they varied in the specificity with which they described and defined these outcomes.

In contrast, the determinant framework analyzed here (HEIF)[67] provides an explicit means to identify barriers to program implementation throughout all stages of population genetic screening. Similarly, the evaluation framework (RE-AIM extension)[71] detailed indicators and health equity considerations for monitoring program outcomes relevant to all program stages.

To make the best use of the variety of recommendations brought up by the different frameworks, these frameworks may best be used in tandem. For instance, determinant domains can be used when process model steps suggest identifying implementation barriers and specific indicators can be drawn from evaluation frameworks when steps call for assessing implementation outcomes.

Among the process models, Proctor reframed,[68] Transcreation,[69] and EquIR,[70] another main concept was the importance of involving community partners and other stakeholders throughout implementation. Such collaboration allows researchers to learn more about local customs and build trust with community members.[81,82] Interventions can better be tailored to a specific population and integrate relevant perspectives, norms, and social and cultural values.[81,82] As a result, this may improve intervention acceptability and effectiveness and prevent health disparities from emerging.[81,82]

Beyond central characteristics, guidance in the later stages of population genetic screening programs, such as follow-up care and cascade screening, was limited. For true public health impact, individuals receiving positive screening results must have access to prevention services to delay or prevent disease onset. Health benefits may also be seen if genetic risk information is communicated to biological relatives. However, frameworks lacked specific guidance about how to ensure equitable referrals to follow-up care or promote adherence to recommended medical interventions. Discussion about sharing health insights and how to engage biological relatives who may be implicated by an individual's risk results was also missing. This is not entirely surprising given that these frameworks were not specifically developed with genetic services in mind but demonstrates that some considerations specific to genetic testing are not addressed by the current literature.

Additionally, implementation frameworks emphasizing health equity have limited guidance for ongoing programs with continuous recruitment beyond high level recommendations to continue to adjust interventions to fit population settings. While the cyclical nature of EquIR[70] and ongoing evaluation measures provided by RE-AIM[71] can be utilized to some extent, guidance particularly relevant to genetics again appears to be absent. For instance, frameworks provide little assistance when thinking about how to incorporate new risk information over time or how to ensure that providers are up to date on genetic recommendations so that they can best advise their patients.

Population genetic screening health equity considerations

Synthesizing findings from the included frameworks, we have compiled a list of relevant health equity questions and outcomes that warrant consideration during the implementation of

population genetic screening programs in order to limit health disparities (Table 4.4). Though not exhaustive, questions may be useful throughout the design and implementation of future screening programs and spur further discussion related to pursing health equity. Broadly, considerations include thinking about the accessibility and cultural sensitivity of different population screening processes. Outcomes focus on understanding the distribution of benefits and harms from genetic screening, and the acceptability of program procedures across various demographic groups.

Table 4.4: Health equity considerations for population genetic screening programs

Stage	Health equity-focused questions	Outcomes assessed across social determinants
Recruitment	• If recruitment occurs in-person, is it at an accessible location? Do people have adequate transportation to the site? Are these physical spaces accessible to people with disabilities, including movement, hearing, vision, etc.? • If recruitment occurs online, how can people without regular internet access be reached? • What are relevant cultural beliefs about genetics in specific population groups? Are recruitment materials designed with these in mind? • What language are informational and consent materials provided in? Does this align with people's preferred language? • How does socioeconomic status and insurance coverage influence screening enrollment? • How does a history of harms influence screening enrollment?	• Number of people offered screening • Number of people who agree to screening • How do people (e.g., health professionals, community members) perceive screening? • Are recruitment and outreach procedures considered acceptable? • Does pre-screening information lead to informed decision-making about screening?

	• If screening is offered by providers, is it offered equally? What provider or patient factors influence if screening is offered?	
Sample collection	How does sample collection occur? How to these procedures restrict access? E.g.: • If sample collection takes place in-person, is it at an accessible location? Do people have adequate transportation to the site? Are these physical spaces accessible to people with disabilities, including movement, hearing, vision, etc.? Does collection take place during routine care? • If sample collection occurs at home, do people have a regular address a collection kit can be sent to and a mailbox for return? • What are relevant cultural beliefs about genetics in specific population groups? Are sample collection and retention procedures designed with these in mind? • What language are materials about sample collection procedures provided in? Does this align with people's preferred language?	• Proportion of people who provide a sample among those who want to receive screening • How do people (e.g., health professionals, community members, stakeholders) perceive the sample collection process? Are procedures considered acceptable? • How easy was it for people to collect samples? If needed, how easy was sample recollection?
Return of results	How do return of results procedures occur? How to these procedures restrict access? E.g.: • If return of results occurs in-person, is it at an accessible location? Do people have adequate transportation to the site? Are these physical spaces accessible to people with disabilities, including movement, hearing, vision, etc.? • If return of results occurs online or via phone, how can people without regular internet or phone access be reached?	• Proportion of people who receive results among those who provide samples • Proportion of people who indicate experiencing psychosocial harms among those who receive screening results

	• What are relevant cultural beliefs about genetics in specific population groups? Are clinical services provided with these in mind? • What language are clinical services provided in? Does this align with people's preferred language? • Do all people with the same screening results receive the most appropriate level of guidance?	• How do people perceive the return of results process? Is the guidance provided acceptable? • How helpful or useful do people find the information learned through screening? • How much time is present between when people provide samples and when results are returned?
Follow-up care & prevention	Are all individuals able to act on screening results, if desired? E.g.: • Are necessary clinics or specialists in accessible locations? Do people have adequate transportation to relevant facilities? Are these physical spaces accessible to people with disabilities, including movement, hearing, vision, etc.? • How does socioeconomic status and insurance coverage influence prevention uptake? • Are all people with the same risk profiles referred to the same type of specialists or advised in the same way?	• Proportion of people who discuss results with their provider among those receiving screening results^ • Proportion of people who meet with appropriate specialists among those who receive positive risk results • Proportion of people who adhere to appropriate medical interventions among those who receive positive risk results • Proportion of people who experience

		psychosocial harms or clinical harms^
Cascade screening	How is genetic risk communication facilitated? E.g.: • Are genetic services accessible to biological relatives? • How do health beliefs, health literacy, and family dynamics influence how genetic risk is discussed within families? • Are all individuals offered the same support regarding risk communication? • What are local/state considerations for cascade screening (e.g., related to sharing genetic information)?	• Proportion of people who discuss genetic risk with biological relatives among those receiving screening results^ • Number of biological relatives who receive testing • How do people view genetic risk information sharing? Is such sharing considered acceptable?
Overall considerations	• Are community partners and other stakeholders involved in program planning, design implementation, and evaluation? • What processes are in place to facilitate program adaptations?	• To what degree do community partners or stakeholders report understanding of and involvement in program processes, trust in research partners, or benefits from program implementation? • How often are program procedures reviewed? By whom are they reviewed? • After receiving screening, would people recommend screening to others?

^Consider by type of screening result (e.g., positive or uninformative)

One of the overall considerations for pursuing health equity is involving community partners. As members of the community are likely more in-tune with local settings compared to researchers, they may be better equipped to understand and identify drivers behind complex inequities.[83] Through community engagement, researchers and public health professionals can ascertain what communities identify as problems to be addressed and what community health priorities are.[83] This can inform if population genetic screening is a suitable intervention in a particular setting and truly meeting community needs. Investment by communities in population genetic screening programs can also promote sustainability of such programs.

Even with these health equity considerations identified, challenges may emerge when incorporating these ideas into practice. For example, answers to these questions may vary by communities included in a single population screening program. Resource constraints may also prevent the adoption of more equitable practices. Additionally, outcome measures may be difficult to ascertain as they may involve time-intensive data collection and the continued engagement of people who have taken part in genetic screening. As such, researchers and health professionals looking to implement screening programs may benefit from using these considerations to appropriately plan and allocate resources.

Examples from current population genetic screening programs

Practices demonstrated by population genetic screening programs in the United States can also provide insight into how some of the above health equity considerations can be employed during program implementation. In the recruitment stage of population genetic screening, lessons can be learned from the Alabama Genomic Health Initiative (AGHI), a genomics research program funded by the state of Alabama with a goal of understanding the

efficacy of population genetic screening among adults.[17] To increase enrollment of African American individuals, AGHI has engaged with faith-based organizations and held outreach events at community health fairs.[17] In addition, AGHI has also found that pop-up enrollment clinics ease logistical barriers by bringing enrollment information and opportunities directly to communities. This, in turn, has helped them increase enrollment from historically underserved populations.[17]

Additionally, The Healthy Nevada Project, a population genetic screening study for Nevada residents, also provides an example of how to incorporate a community's preferred language during recruitment.[15] This program has hosted a recruitment event with Spanish consent forms, signage, and Spanish speaking staff to assist with enrollment of members of the local Hispanic community.[15]

Finally, the Geisinger MyCode Community Health Initiative (MyCode), an electronic health record-linked biobank, has measured reach to understand the representativeness of those who consented to the return of genetic results.[84] This analysis found that individuals who consented were more likely to be female, White, Non-Hispanic, and have a Geisinger health plan and physician than those who declined participation in the program or withdrew consent after finding that results would be returned.[84]

Regarding sample collection, flexible procedures best suited to individual needs have been adopted by The University of Vermont Medical Center, which is offering genetic testing related to cardiovascular and cancer disease risk.[85] In particular, this program allows either in-person or at-home sample collection, rather than mandating a certain collection procedure. To simplify sample collection, other programs, such as MyCode and a screening program in South

Carolina (In Our DNA SC), also collect samples for testing during routine care appointments to reduce barriers to screening.[14,86]

In the screening study conducted at the UWMC (described in Chapter 2), flexible policies surrounding sample collection and retention were also designed to promote screening enrollment. In particular, individuals were allowed to provide a sample for genetic screening without consenting to having their sample stored in a biobank.

Return of results processes in existing programs have also been informed by community partnerships. For example, by holding focus groups with patients, clinicians, and community members throughout the program's service area, MyCode researchers have been able to gather feedback about current implementations and future directions.[14,87] These focus groups have been used to assess if participants would like to receive medically actionable genetic risk results and have these results added to their medical record.[88] Based on these discussions, MyCode has altered their research protocol to allow for return of results to participants.[88]

Limitations

Our study may have been limited by the frameworks considered for analysis. Due to stringent inclusion criteria, we may not have identified all relevant frameworks. In addition, though we give a broad overview of implementation science frameworks that center health equity, we did not assess the quality of these frameworks. However, our analysis of how frameworks have been used in other settings provide an indirect measure of utility and quality. Our assessment of framework applicability to population genetic screening programs may also have been limited. Relevant stages, such as sample lab testing, were not included and some of our analysis may be applicable to multiple stages. Despite these limitations, our study is a first

step in describing the current state of implementation science frameworks that explicitly focus on health equity and how they can be applied to improve the equitable implementation of population genetic screening programs.

4.6 Conclusion

Current implementation science frameworks that emphasize health equity offer broad recommendations applicable to the implementation of population genetic screening programs. However, gaps still exist in guidance provided for stages of population genetic screening that are ongoing, such as follow-up care and cascade screening. Through our application of frameworks to population genetic screening, we have created a list of considerations and outcomes that may assist with more equitable implementation. These include thinking about if program procedures are accessible and acceptable, and if benefits and harms from screening are distributed evenly. Researchers planning to implement screening programs may benefit from consulting these considerations or following guidance from analyzed frameworks.

Chapter 5: Conclusion

While population genetic screening has the potential to have a large public health impact, several aspects of this strategy need to be explored. Findings from this dissertation add to our understanding of attitudes toward population genetic screening among an unselected and diverse population, barriers to enrollment and the pursuit of follow-up care, and considerations for planning, designing, and implementing more equitable screening programs in the future. This work can be used to inform overall assessments about widespread population genetic screening program implementation.

In Chapter 2, we examined enrollment in genetic screening overall and across race and ethnicity groups using data from a population genetic screening research study conducted at the UWMC. We found that enrollment in this screening study among an unselected and diverse cohort and using a low-touch approach without remuneration was quite low (7%) compared to past screening trials. Differences in enrollment were seen across race and ethnicity groups. These differences mimic past patterns of differential utilization seen in genetic healthcare settings, suggesting that many of the social issues that have contributed to health disparities related to genetic services are not readily alleviated by population genetic screening programs, or at least this particular implementation. In this chapter, we also identified reasons related to declining participation in genetic screening. These reasons included risks overshadowing benefits, not wanting to know genetic risk results, and challenges with screening logistics. Results from this chapter demonstrate that many process barriers may interfere with the equitable implementation of population genetic screening. Findings from this research offer useful information for the design of future population genetic screening programs by demonstrating the need to remove logistical obstacles to screening enrollment.

In Chapter 3, we explored the experiences of adults who received positive results through the population genetic screening study at the UWMC with a focus on psychosocial impacts of results, pursuit of follow-up care, and overall opinions on screening. Results showed that psychosocial impacts from results were similar between people who were aware of genetic risk prior to screening and those who were not, with harms being limited overall. Participants found screening results useful for personal and familial health but expressed a desire to streamline the follow-up care and prevention processes. Our results highlight a need to distinguish screening from diagnosis at the time of informed consent to minimize psychosocial impacts and to provide support for individuals not just during initial screening and result return, but later in follow-up and prevention stages. Specifically, genetic screening programs will more successfully promote disease prevention if they provide clinical confirmation of screening results, facilitate appointments with appropriate specialists, encourage communication with primary care providers or incorporate screening into existing health services managed by providers, and supply educational resources for such providers.

In Chapter 4, we identified and described currently available implementation science frameworks that explicitly consider health equity and assessed their applicability to population genetic screening. We found that current frameworks offer broad recommendations applicable to the initial implementation of population genetic screening programs. However, gaps exist in guidance for ongoing processes such as follow-up care and cascade screening, and for program features specific to genetics. Through our analysis of frameworks, we created recommendations for health equity questions and outcomes to consider to improve equity in population genetic screening program planning, design, and implementation. These include thinking about if program procedures are accessible and acceptable, and if benefits and harms from screening are

distributed evenly. Results from this chapter can be used by researchers looking to prioritize health equity during genetic screening and can inform where efforts may best be directed to reduce health disparities in population screening settings.

Reflections on the population genetic screening research study at the UWMC

Findings from this dissertation work can be used to evaluate the genetic screening research study at the UWMC. Suggestions for changes to be adopted by future programs and reflections on practices to continue are given by each stage of population genetic screening below. Lab testing will not be included as this stage is not patient facing and was not an area of emphasis in this dissertation work.

Recruitment

While the genetic screening study at the UWMC employed limited outreach efforts, future programs would benefit from more concerted efforts to intentionally inform people about population genetic screening. The email recruitment method used in the genetic screening study is a low-cost way to invite people for screening but faces challenges regarding perceived legitimacy. Additionally, emails can often go unread, and many people invited for screening through the study at the UWMC may not have been aware of the invitation.

Genetic screening mediated by a provider can address some of these issues. Offering screening through a clinical practice can remove concerns related to legitimacy and conversations with providers can promote overall awareness about screening. Provider mediated screening can also improve informed decision-making. While invitees of the genetic screening study at the UWMC were able to contact study staff in the case of questions, the opportunity for asking questions may more naturally emerge in discussions with a provider or clinic staff.

Future screening programs can adopt the condensed pre-screening information approach used by the genetic screening study at the UWMC by providing information about genetic screening benefits and risks, prior to visits with a provider. This pre-screening information should also highlight the non-diagnostic nature of screening, genes and conditions being screened for, and the limitations of screening. By providing this information prior to speaking with a provider, time with a provider can be optimized.

Sample Collection

The at-home DNA saliva collection method employed in the genetic screening study at the UWMC allowed for wider screening reach, particularly during a global pandemic. Future programs may benefit from employing this at-home sample collection method as well as having an in-person option. The flexibility in this dual approach can promote screening as different sample collection methods may be better suited for different people depending on circumstance.

Offering an in-person option for sample collection, particularly if it occurs during routine care, can also facilitate screening among those who are interested in this genetic knowledge but fail to prioritize at-home sample collection. Many people in the genetic screening study at the UWMC reported losing their kits, forgetting to provide a sample, or difficulties providing a sample, and such issues may be addressed by taking the responsibility of sample collection off the individual. An in-person sample collection option can also act as a backup means of sample collection if DNA collected through an at-home saliva kit is of poor quality.

Return of Results

The return of results practice adopted by the genetic screening study at the UWMC was a low-cost and efficient way to deliver results to screening enrollees. Genetic counselors delivering positive screening results over the phone or through telehealth services eliminates the need for

people to travel to a specific location, which is of benefit to people who face time or transportation constraints. The genetic screening study approach of delivering uninformative results through an online portal also saves genetic counselor time and by providing everyone with the option to speak with study staff as needed, genetic counselors were still available to screening study enrollees.

If screening were to be incorporated into clinical practice, as discussed above, the return of results process could potentially be strengthened further. Depending on provider education, providers can lead return of results processes but rely on genetic counselors in more challenging cases. As providers may be in more regular contact with patients than a genetic counselor, this can promote continued conversations about genetic results, as needed, which may assist with improved understanding about implications of genetic results (both for positive and uninformative results). The integration of providers into the return of results process also removes the additional task of individuals communicating results with their provider and can facilitate recommended changes to medical care.

Follow-up Care

As the genetic screening study at the UWMC was a research study, enrollee genetic results were not added to their medical record. Given issues with the clinical confirmation process after the return of research screening results reported in this dissertation work, future population genetic screening programs would benefit from providing such confirmation. Lack of clinical confirmation creates a hurdle people must cross before engaging in prevention efforts. For people who have limited time to devote to health practices, have issues with insurance when trying to pursue clinical confirmation, or question the necessity of confirmation, this hurdle can derail recommended health care changes based on their genetic result.

Preventive Interventions

While the genetic screening study at the UWMC did not extend through the preventive interventions stage of screening, future screening programs should provide more support in this area to facilitate recommended medical interventions. Provider mediated genetic screening can potentially assist with this step as well. As providers will already be informed about positive screening results, this can simplify referrals to specialists. Additionally, people will already be plugged into health systems that may be able to streamline any preventive care. To assist providers with recommended changes to care, future population genetic screening programs may benefit from creating standard recommendations for given genetic findings that providers can follow.

Cascade Screening

The genetic screening study at the UWMC informed people with positive screening results about another research opportunity designed to encourage communication about genetic risk among families. Future programs would benefit from also encouraging family communication as cascade screening built on top of a population genetic screening program can identify more at-risk individuals. To promote cascade screening, screening programs can provide informational material designed to guide conversations with relatives or recommend services or research studies that assist with family communication about genetic risk.

Looking forward

While the previous section describes suggestions for future population genetic screening programs, these suggestions, in addition to other questions related to population genetic screening, require further investigation before genetic screening is ready for widespread

implementation. Large genetic screening pilot programs are needed, particularly in clinical settings, to vet some of the ideas presented above. Some questions of interest to explore in these pilot programs are listed below:

- Which populations are missed by a population genetic screening approach mediated by a provider? How can reach be improved?
- What are patient perspectives on genetic screening offered in a clinical setting?
- What are provider perspectives on genetic screening offered in a clinical setting? What types of provider support and education are needed for provider mediated screening?
- What staffing needs are required to support population genetic screening (e.g., how many genetic counselors, specialists)? Which populations may be impacted by limitations in staffing and how might these be addressed?
- What infrastructure is needed for screening and subsequent prevention (e.g., are clinics offering mammograms available)? Which populations may be impacted by limitations in infrastructure and how might this be addressed?
- What is the effect of population genetic screening on health outcomes?
    - For individuals with positive risk results: Do health care plans change? Does disease prevention occur? Are medical interventions unnecessary in some cases? How do answers to these questions vary across social dimensions? How does a genetic knowledge base that is biased toward people of European ancestry impact health outcomes?
    - For individuals with uninformative risk results: Do genetic results lead to negligence of recommended routine prevention practices? How can return of results processes best mitigate this?

- What is the protocol for determining which genes are included in population genetic screening (e.g., what evidence level is needed)? How often are genes re-evaluated and considered for inclusion (or removal)?
- How often are results from genetic screening re-evaluated to incorporate emerging genetic knowledge? How are significant re-evaluated results returned to individuals?
- Is genetic screening cost effective?
    - What genes/how many genes would a screening panel need to include for screening to be cost effective?
    - At what age is genetic screening most cost-effective?
- How might upfront patient costs for genetic screening impact enrollment?
- How might the routinization of genetic screening affect personal decision-making about screening?
- Is population genetic screening aligned with community health priorities?

We hope that these considerations, along with others described in this dissertation, are investigated and incorporated when making decisions about population genetic screening, designating public health priorities, and allocating resources so that strides can be made in improving health for all people. As we seek to pursue health equity in the context of population genetic screening, we must recognize that this is only one component in advancing health equity.[89] As such, a true consideration of health equity may go beyond limiting disparities in population genetic screening but will seek to understand the role of genetics in furthering an overall health equity agenda.

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Appendix

Study information and frequently asked questions provided by the population genetic screening study at the UWMC

Study Information

Q. What do I have to do to join the study?
A. First, you have no obligation to join this or any research study. There are no negative consequences if you do not want to join. For any questions you can call Dr. Brian Shirts and the study team at (206)685-1176 or e-mail geneticscreening@uw.edu.

We must collect your DNA for testing. In a week or two, a saliva collection kit with instructions and consent forms will be sent to you via mail. Please read the consent forms carefully. Return the saliva kit and signed consent forms in the return, postage paid, envelope provided. We get less than a teaspoon of saliva samples. **We cannot receive the saliva sample or test your DNA without the signed consent forms.**

To learn more about this research study, please read the following information. You will be asked a few questions in the next few screens.

Q. What information do you need?
A. We need to know your address and phone number to send you a saliva DNA collection kit and consent form.

Once we receive your sample and consent form in the mail, we will ask you to fill out more questions to tell us about your feelings around genetic testing. This survey will take no more than 20 to 30 minutes to complete. You can skip any questions you would rather not answer.

Frequently Asked Questions

Q. How long will the DNA results take?
A. DNA research testing results take a while. It is our goal to get results to all participants within 6 months or sooner. After receiving your results, your participation is complete. However, you are free to contact the Researchers at any time.

Q. What kind of results will I get?
A. Most people will find that they do not have increased risk for inherited disease that can be identified by this screening test. Those people will get an e-mail allowing them to look up their results on a secure study website or can opt to receive a mailed letter with their results. While these results are reassuring, they do not mean that there is no disease risk; it means that there is no increased risk that can be detected by the genetic screening test used in this study.

About one or two percent of people will get a “higher-risk” result. These people will receive a phone call or e-mail from a study Genetic Counselor or the Investigator to discuss the results. This test just measures risk (or chance) of developing a disease. Not everyone with a “higher-

risk" result is certain to develop the disease. Because we conduct a screening test that will not go in your medical records, the results should be confirmed with follow-up clinical testing through your doctor. Printable "higher-risk" result reports will be available to you on the secure website so that you can share them with your doctor.

Q. What about other genetic studies?
A. Everyone that participates in this study can also join the University of Washington – Brotman Baty Precision Medicine Institute (BBI) Biorepository and Registry Study. A repository collects and stores samples and data to be used for future precision medicine research. A registry is a list of names of people who don't mind being contacted occasionally to hear of new research. If you are interested in joining the BBI Repository/Registry study you can indicate this on a separate paper consent form that you will receive with the saliva DNA collection kit.

People who have a "higher-risk" result will also be eligible to join a study to learn more about their genetic risk, and also involve family members who may share their genetic risk.

Q. Will my information be kept confidential and safe?
A. All information you provide us will be confidential and we will make every effort to keep your information and samples safe.

Q. How long will my samples and information be saved?
A. Your samples may be saved indefinitely.

Q. What if I change my mind?
A. You can contact us at any time to remove your information/sample from the study or tell us to not return results to you.

Q. What are the risks for me joining this study?
A. It may be unpleasant to collect a sufficient amount of saliva (spit) for the DNA test. Learning about your genetics can be emotionally stressful. Some people cannot predict how learning genetic information may make them feel until after they have received the results. Talking about private matters and personal feelings may make you feel uncomfortable or embarrassed. Another possible risk is loss of confidentiality or private information should a data breach occur. We will do our best to help you understand your genetic results and to keep your private information secure.

Although The Genetic Information Nondiscrimination Act of 2008 federal law (GINA) has been passed to prevent discrimination based on genetic information, it is possible that taking part in this study might make it harder to gain and/or keep employment or insurance. If you have any questions about your rights as a research participant, you can contact the University of Washington Human Subjects Division at (206)543-0098 or call collect at (206)221-5940.

Q. What are the benefits for me joining this study?

A. We cannot predict if you will receive personal benefit from participating in this research. Our hope is that you will gain information on your genetic risks for a screening list of inherited diseases. Your participation may benefit society by helping to advance genetic science. We are hopeful that future generations may benefit from the scientific and medical knowledge we gain, and that better methods will be put in place to start using genetic information to prevent disease.

Q. Will I get paid for this study?
A. No.

Q. Does this study cost me anything?
A. No. The genetic screening test is free. Any follow-up medical care will not be covered by the study.

Q. Who is funding this research
A. This is funded by the Brotman Baty Institute for Precision Medicine at the University of Washington.

Semi-structured interview guide used for data collection in Chapter 3

MOTIVATION FOR PARTICIPATION

1. Why did you choose to participate in the genetic screening study?

2. Separately, why did you choose to participate in my study where we'll explore your opinions about genetic screening?

3. Did you have any concerns before deciding to join the genetic screening study?
   If yes, what were they?

4. Who, if anyone, did you consult with when deciding whether or not to join the study?

IMPACT OF GENETIC RESULTS

5. Walk me through what it was like to get your results.

6. How did you feel?

7. What, if anything, surprised you about getting your results?

8. Who, if anyone, did you talk with about your results?
   Family, friends…
   How did that go?

9. How has getting these findings affected your life?
   Your well-being?
   Your family?
   Any other changes?

HEALTH BEHAVIOR & BARRIERS TO CARE

10. Have you changed anything about your lifestyle because of this result?
    If so, what? (diet, exercise, smoking)

11. What follow up care have you pursued?

12. Have you spoken to any health care providers outside of the study?
    Physician? Genetic counselor? Alternative care providers? Mental health?
    How did that go?

13. How difficult was it for you to speak with a provider outside of the study for follow up?

14. Did getting your results have any financial costs to you or your family?
    If yes, can you tell me more about those? (Visits to the doctor, tests or medications, diet changes, etc.)

15. Does your health insurance cover the costs of follow up testing & related appointment?
    How easy has it been to get your follow up care covered?

16. If care was not covered…
    Can you tell me more about that?
    How has this affected your future health plans?

17. If no follow up care has been pursued…Can you tell me a bit about why you have not pursued follow up care?

REFLECTION

18. Looking back, how do you feel about your decision to participate in the study?

19. Would you recommend the study to others?
    Why or why not?

20. Do you think it would be better if you had more information before testing?
    What information would have helped you before testing?

21. Do you think it would be better to have more guidance after testing?
    What other guidance would you have liked after testing?

22. Have you searched for any information about your genetic result independently?
    If yes, can you tell me a bit about that?

23. How do you think this screening program can be improved?

CONCLUSION

24. Is there anything else you would like to share about your experience with genetic screening?