THE UNIVERSITY OF CHICAGO

GENETIC AND ENVIRONMENTAL SUSCEPTIBILITY TO CANCER IN UNDERSTUDIED POPULATIONS AND NOVEL INTERVENTIONS TO REDUCE RISK

A DISSERTATION SUBMITTED TO

THE FACULTY OF THE DIVISION OF THE BIOLOGICAL SCIENCES

AND THE PRITZKER SCHOOL OF MEDICINE

IN CANDIDACY FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF PUBLIC HEALTH SCIENCES

BY

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CHICAGO, ILLINOIS

DECEMBER 2023

To my husband, for becoming an academic by association. Thank you for your unconditional love, support, and unwavering faith in me.

and

To my parents, gracias por su apoyo y amor incondicional, por estar a mi lado en cada paso de mi camino académico y por creer en mí incluso cuando dudaba de mí misma. Han sido mi ejemplo de perseverancia y trabajo arduo, demostrándome que con determinación y esfuerzo se puede alcanzar los sueños más grandes.

and

To my sister, for unknowingly pushing me to always strive for my best to make you proud.

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ACKNOWLEDGEMENTS

I would like to express my heartfelt gratitude to the individuals who have provided unwavering support, guidance, and expertise, shaping my growth and development throughout my journey in graduate school and profoundly influencing the work presented in this dissertation.

First and foremost, I would like to express my sincere thanks to my advisor, Dr. Brandon Pierce. Being taught and mentored by Dr. Pierce has been transformative, enabling me to evolve into the scientist I am today. His exceptional knowledge, intellectual rigor, and unwavering commitment to scientific inquiry have not only shaped my research but also inspired me to pursue excellence in every aspect of my academic journey. I am truly grateful for his invaluable guidance, constructive feedback, and constant encouragement. Thank you for believing in me, supporting my applications, and writing so many letters of recommendation. Your belief in my potential means the world to me.

Additionally, I would like to express my heartfelt appreciation to my co-advisor, Dr. Laura Fejerman. Collaborating with Dr. Fejerman since my time as an MPH student has been a continuous source of inspiration. Her brilliance as both a scientist and an individual has guided my research endeavors. As a Latina genetic epidemiologist, she has served as a beacon of representation, a rare and much-needed presence in the field. Working alongside Dr. Fejerman guided me towards the field of genetic epidemiology and significantly influenced my decision to pursue a PhD. Her mentorship, unwavering support, and dedication to fostering a diverse and inclusive scientific community have played instrumental roles in my academic and personal growth.

I am also immensely grateful to my entire dissertation committee, Drs. Aresha Cardoso-Martinez (chair), Lin Chen, and Habibul Ahsan, for their invaluable insights, thoughtful critiques, and constructive suggestions. Their expertise and commitment to my academic development have significantly enhanced the quality and rigor of my research.

Furthermore, I would like to extend my appreciation to the faculty and staff of the Department of Public Health Sciences for cultivating a vibrant and intellectually stimulating academic environment. Your passion, dedication to research, and willingness to share knowledge have enriched my educational experience and broadened my horizons. Special thanks to Michele Thompson for her invaluable support and contributions to our program. I would also like to acknowledge Ryan Carter for his assistance with numerous technical support issues that always seemed to arise near deadlines.

My deep gratitude goes to my lab mates and fellow graduate students, past and present, for providing a supportive and collaborative community throughout my doctoral journey. Your friendship, encouragement, and shared experiences have played a pivotal role in my growth as researcher as well as a friend.

I would also like to thank Dr. Ronald Hershow, Director of the Epidemiological and Biostatistics Division at UIC SPH, whose guidance, mentorship and belief in my research abilities were what allowed my journey to begin.

Lastly, I am profoundly grateful to my parents, sister, husband, and friends for their unwavering love, encouragement, and belief in my abilities. Your support has been a constant source of strength and motivation.

ABSTRACT

This dissertation explores the interplay between genetic and environmental factors in cancer susceptibility while addressing disparities in underserved populations. It comprises three chapters that shed light on different aspects of cancer research and intervention.

Chapter 1 focuses on the impact of genetic variation on arsenic metabolism and toxicity susceptibility. Genome wide association analyses identified genetic variants associated with arsenic species in urine and blood samples, revealing insights into the complexity of arsenic metabolism and the genetic factors influencing toxicity risk.

Chapter 2 investigates the effects of returning personal genetic information on arsenic toxicity susceptibility in rural Bangladesh. Participants categorized using Polygenic Risk Scores receive information on arsenic effects and exposure reduction strategies. While the intervention increases self-reported behaviors aimed at reducing exposure, it does not significantly reduce urine arsenic levels beyond the impact of an educational intervention alone. This study contributes to our understanding of genetic factors impacting arsenic metabolism and provides valuable insights into returning genetic results in resource-limited settings.

Chapter 3 shifts the focus to breast cancer, the most common cancer among women in the United States and a leading cause of cancer death among Hispanics/Latinas (H/L). It highlights the lower likelihood of early-stage diagnosis in H/L women compared to Non-Hispanic/Latina White (NHW) women and the disparity in genetic testing uptake for inherited breast cancer mutations. To address this gap, the "Tu Historia Cuenta" program was developed, targeting monolingual Spanish-speaking individuals in California. This program raises awareness about

hereditary breast cancer, provides educational resources, and facilitates access to genetic counseling and testing services.

By addressing diverse aspects of cancer research and intervention, this dissertation enhances our understanding of the genetic and environmental determinants of cancer susceptibility, highlights disparities in underserved populations, and offers insights into novel interventions to reduce cancer risk. It emphasizes the importance of tailored approaches that consider the unique needs and circumstances of diverse populations, ultimately striving for equitable and effective cancer prevention and care.

Chapter 1 GENETIC VARIATION IN THE FMO AND GSTO GENE CLUSTERS IMPACTS ARSENIC METABOLISM IN HUMANS

1.1 INTRODUCTION

Inorganic arsenic (iAs) is a human carcinogen[1], and exposure to iAs affects >200 million individuals worldwide through drinking water.[2, 3] In Bangladesh, >50 million individuals are chronically exposed to iAs through drinking-water from naturally-contaminated wells that have some of the highest iAs concentrations reported in the world.[3, 4] Chronic exposure to iAs above the World Organization (WHO) safety standard (>10 µg/L) increases the risk for a wide array of diseases, including cancer.[5, 6] The excess risks of cancer associated with lifetime exposure to arsenic is more than 100 times higher than other known carcinogens at concentrations >10 µg/L.[7] Among individuals chronically exposed to iAs, the risk for arsenic-related diseases and mortality remains high for several decades even after cessation of exposure.[8, 9] The most common sign of toxicity caused by iAs exposure are skin lesions, which appear as hyperpigmentation during early exposure and keratosis at advanced stages of exposure.[10]

The liver is the primary site for the metabolism of ingested inorganic arsenic (iAs). One important metabolic pathway involves the reduction of pentavalent iAs (As^{V}) to trivalent iAs (As^{III}),[11] followed by oxidative methylation mediated by arsenic methyltransferase (AS3MT). This enzymatic process leads to the production of monomethylarsonic acid (MMA^{III}) as an intermediate. Subsequently, a second methylation reaction occurs, resulting in the formation of dimethylarsinic acid (DMA^{V}).[12] DMA has a shorter half-life in circulation and is more readily eliminated in urine compared to MMA and iAs.[13, 14] Consequently, DMA constitutes the majority

of excreted arsenic species.[15, 16] Hence, an individual's arsenic metabolism efficiency (AME) can be defined as their capacity to methylate arsenic and generate DMA. The percentage of DMA among the total arsenic species in urine (DMA%) is commonly used as an indicator of AME.[17-19]

There is inter-individual variation in arsenic metabolism efficiency due to underlying genetic differences, [4, 20-25] and this variability impacts the internal dose of arsenic and toxicity risk. Various factors, including age, sex, body mass index and smoking status, and environmental exposure, contribute to individual variations in arsenic metabolism and internal dose concentrations.[26] Prior GWAS of Bangladeshi individuals have identified independent associations of four SNPs (single nucleotide polymorphisms) with AME: three in the 10q24.32/AS3MT region (rs4919690, rs11191492, and rs191177668) and one in the FTCD gene (rs61735836), a gene involved in histidine catabolism.[19, 27-29]

The *AS3MT* and *FTCD* gene regions are known to influence susceptibility to arsenic toxicity, other genetic factors contributing to arsenic metabolism and toxicity risk (i.e., skin lesions) are believed to exist.[4, 20] Given the significant global health impact of arsenic exposure and the variability in arsenic metabolism efficiency among individuals,[30, 31] our objective is to identify genetic determinants associated with arsenic metabolism and toxicity phenotypes. Although no other regions of the human genome, besides *AS3MT* and *FTCD*, have robust evidence of association with arsenic metabolism efficiency, studies of heritability suggest the existence of additional variants.[32, 33] In order to identify additional genetic variants that influence arsenic metabolism efficiency, we conducted a the largest genome wide association study (GWAS) in urine to date and first GWAS in blood to look at the inherited genetic variation and its effects on arsenic metabolism and toxicity.

1.2 METHODS

1.2.1 Study Participants

DNA samples were obtained at baseline recruitment from The Health Effects of Arsenic Longitudinal Study (HEALS)[34] and the Bangladesh Vitamin E and Selenium Trial (BEST).[35] The HEALS cohort is prospective study of health outcomes associated with arsenic exposure through drinking water of adults in located in Araihazar, Bangladesh, a rural area with substantial exposure to arsenic through naturally contaminated drinking water from local wells. HEALS began in 2000, is comprised of >20,000 adult participants (followed over 15-20 years to ascertain health outcomes), of which 6,540 have genome-wide SNP data. Trained study physicians conducted in-person interviews, clinical evaluations, and urine collection at baseline follow-up visits. BEST is a randomized chemoprevention trial evaluating effects of vitamin E and selenium supplementation on skin cancer risk among arsenic-exposed individuals. BEST participants are residents of Araihazar, Matlab and surrounding areas in Bangladesh. BEST has 7,000 adult participants (all with skin lesions at baseline) and 1,990 have existing genotype data. BEST uses many of the same study protocols as HEALS, including arsenic exposure assessment and biospecimen collection.

Some HEALS participants also participated in ancillary studies which investigated correlates of AME and folate interventions to increase AME. For this study, we used data from 1,099 genotyped HEALS participates who additionally participated in one, or more, of three such studies: Nutritional influences of Arsenic Toxicity (NIAT, n=163), the Folic Acid and Creatine Trial (FACT, n=595), or Folate and Oxidative Stress (FOX, n=341). These studies all measures participants' arsenic and arsenic metabolite concentrations in both blood and urine. Data on

blood arsenic species were available for 977 of the 1099 genotyped individuals for the NAIT (n=110), FOX (n=273) and FACT (n=594) studies. Blood was collected at baseline (Week 0) for FOX, at Week 0 and 5 for NIAT, and at Weeks 0, 1, 12 and 24 for FACT. Urine was collected at Week 0 for FOX, weeks 0 and 5 for NIAT, and Weeks 0, 1, 6, 12, 13, 18, and 24 for FACT. Bio-specimen measurements were averaged when data from multiple time points was available.

1.2.2 Measurement of Total Arsenic

Arsenic exposure was assessed based on arsenic concentrations in urine. Total urinary arsenic concentration was measured by graphite furnace atomic absorption using the Analyst 600 graphite furnace system (with a detection limit of 2µg/L).[36] Urinary creatine was analyzed using a method based on the Jaffe reaction for adjustment of urinary total arsenic concentration.[37] Total urine and blood arsenic was then estimated by computing the sum of arsenic metabolites iAs^{III}, iAs^{V}, MMA, and DMA. Urinary total arsenic was divided by creatinine to obtain a creatinine-adjusted urinary total arsenic concentration, expressed as µg/g creatinine. Urinary total arsenic is a good biomarker of aggregate ingested arsenic exposure, and captures exposure from multiple sources such as water, food, soil and dust.[38]

1.2.3 Arsenic Species

Both urinary and blood arsenic species (i.e., metabolites) were distinguished using a method described by Reuter et al.[39] This method used high-performance liquid chromatography separation of arsenobetaine, arsenocholine, As^{V}, As^{III}, MMA, and DMA followed by detection by inductively coupled plasma-mass spectrometry with dynamic reaction cell. Because As^{III} can oxidize to As^{V} during sample transport, storage, and preparation, we sum these two species to obtain total iAs (i.e., As^{III} + As^{V}). The percentage of iAs, MMA and DMA in total arsenic was calculated after subtracting arsenobetaine and

aresenocholine (i.e., nontoxic organic arsenic from dietary sources) from the total and then dividing the concentration of each species by the total concentration.

1.2.4 Genotype data

6,665 HEALS and 1990 BEST participants have been genotyped using Illumina's HumanCytoSNP-12 (299,140 SNPs), Infinium Multi-ethnic EUR/EAS/SAS arrays (1,475,140 SNPs), or the Global Screening Array (654,027 SNPs). Most participants with data from the HumanCytoSNP-12 also have complementary data from Illumina's exome array. For each array, we removed non-rs SNPs, SNPs with a call rate of <90%, monomorphic SNPs, and samples with a call rate <90%. The Michigan Imputation Server[40] was used to genotype unmeasured SNPs using the Haplotype Reference Consortium (HRC) reference panel.[31] Only high-quality imputed bi-allelic SNPs (imputation r2 > 0.3) and SNPs with minor allele frequency >0.005 were retained (8,711,421 SNPs).

1.2.5 Ascertainment of skin lesion status

HEALS and BEST participants were clinically assessed for skin lesions across the entire body at each study visit. [34, 35] A protocol similar to the quantitative assessment of the extent of a body surface involvement in burn patients[41] was used to quantify the size, shape and extent of skin lesion involvement. The principle is based on dividing the entire body skin surface into 11 segments (e.g., front of arm, back of arm, face) and assigning percentages to each of them based on their size relative to the whole body.[42] There are currently 1458 (prevalent & incident) skin lesion cases and within the HEALS cohort and 1990 cases within the BEST cohort with existing genotype data in this study and 5207 controls (with no history of lesions).

1.2.6 Statistical analysis

Associations analyses for the GWAS of arsenic metabolism efficiency and skin lesions were conducted using mixed linear models as implemented in the GCTA software[43] to account for cryptic relatedness among individuals in our sample (previously described[20]). These models will also be adjusted for age, sex, and genotype batch.

GWAS of skin lesions status was run separately by genotyping batch. There were 4806 participants that were genotyped using the 300k array (2395 cases, 2411 controls), 466 genotyped using the 300k array without exome data (92 cases, 374 controls), 1878 multi-ethnic custom array (789 cases, 1089 controls), 608 multi-ethnic non-custom array (124 cases and 484 controls) and 1133 global screening array (48 cases, 849 controls). The 5 GWAS were then meta analyzed using PLINK 1.9 meta-analysis.

Findings from GWAS analyses were interpreted using Manhattan Plots, quantile-quantile plots and locuszoom plots. We identified SNPs that pass the standard genome-wide threshold (P-value $<5x10^{-8}$). For signals identified, we (1) ensured all QC metrics for identified SNPs were acceptable, (2) searched for secondary signals after adjusting for the top SNP, and (3) examined linkage disequilibrium for the top SNPs.

To investigate the role of identified SNPs in gene regulation we leveraged data on expression quantitative trait loci (eQTL) and splicing QTLs (sQTL) from the Genotype-Tissue Expression (GTEx) project. Genome-wide eQTL studies have shown that eQTLs explain a substantial proportion of variation in gene expression, [44-46]. Furthermore, eQTL analysis for a variety of molecular trains can provide evidence for specific regulatory stages and functions of gene expression.

To help determine whether a common causal variant was responsible for both GWAS and eQTL/sQTL signals at a given locus we used colocalization methods. We used the COLOC R package version 5.2.2. [47] which provides a Bayesian framework to assess the probability of shared causal variants at a given locus for multiple traits using SNP-based summary statistics (from GWAS or QTL studies). Coloc estimates the posterior probabilities of different colocalization hypotheses, such as no colocalization, colocalization with one trait, or colocalization with both traits, based on priors specified in the analysis.

1.3 RESULTS

1.3.1 GWAS of arsenic species measured in urine

GWAS of arsenic species measured in urine (DMA%, MMA%, and iAs%) among 6,540 individuals identified previously reported associations in the AS3MT (DMA% $P=2.4x10^{-51}$) and FTCD (DMA% $P=2.2x10^{-48}$) regions (**Figure 1**). A novel association signal was identified in the FMO (Flavin-containing monooxygenase) gene cluster at 1q34.33, a region containing FMO1, FMO2, FMO3, and FMO4. FMOs metabolize xenobiotic chemicals through oxygenation, but currently there is no established role for FMO genes in arsenic metabolism. The minor allele (A, MAF=6.1%) at lead SNP rs12406572, located in intron 7 of FMO3, was associated with increased urine DMA% (beta=1.62, $P=3.9x10^{-8}$) and decreased urine MMA% (beta=-1.3, $P=3.1x10^{-16}$), but it did not show clear association with urine iAs% (beta=-0.28, P=0.22). There also evidence of a suggestive secondary association signal in this region, particularly for MMA% ($P=6.5x10^{-7}$).

Figure 1-1 GWAS of Urine Arsenic Species Identifies FMO3 Region.

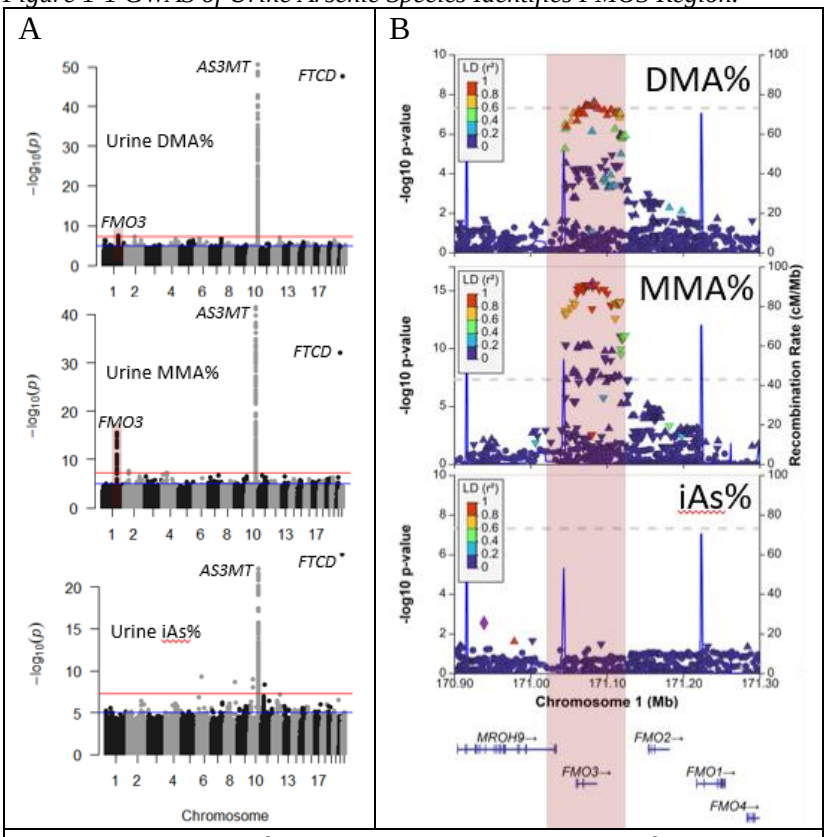


Figure 1. GWAS of Urine Arsenic Species Identifies FMO3 Region. A) Manhattan plots of Urine DMA% and MMA% showing novel association with AME, showing the strongest association in MMA%. B) Locuszoom plot showing FMO3 region

Among the SNPs showing the strongest evidence of association was rs2266780 (MMA% $P=3.2x10^{-16}$), a missense variant in exon 7 of FMO3 that codes for a Glu (E) to Gly (G) amino acid substitution (CADD score of 24.4; SIFT: 0.01/deleterious, PolyPhen: 0.86/possibly damaging). This SNP (MAF=0.061) has been previously reported to associated with trimethylaminuria, a deficiency in FMO3 enzyme leads to a rare metabolic disorder causing a fishy odor.

Among the SNPs showing the strongest evidence of association was rs2266780 (MMA% $P=3.2x10^{-16}$), a missense variant in exon 7 of FMO3 that codes for a Glu (E) to Gly (G) amino

acid substitution (CADD score: 24.4; SIFT: 0.01/deleterious, PolyPhen: 0.86/possibly damaging). This SNP (MAF=0.06) has been previously reported to associated with trimethylaminuria, a deficiency in FMO3 enzyme leads to a rare metabolic disorder causing a fishy odor. The urine MMA% signal at FMO3 also showed strong evidence of co-localization with a splicing (s)QTL for FMO3 in at least 15 GTEx tissue types, including liver (PP4=0.94), adipose (subcutaneous) (PP4=0.98) and lung (PP4=0.98). (**Figure 2**; **Supplementary Table 1**). The MMA%-decreasing allele (A) was associated with decreased excision of the canonical intron 6 (chr1:171110997:171114007) and increased excision of an alternative intron chr1:171110997:171116208. These findings suggest that the genetic variant influence the splicing of FMO3 may play a role in modulating the metabolism of arsenic and contributing to the observed differenced in urine MMA% levels.

In HEALS, the MAF of lead SNP rs12406572 is 6%, consistent with the MAF observed in 1KG BEB group (6%). However, the MAF rs12406572 varies substantially across 1KG populations (3% in SAS, 12% in AMR, 17% in EAS, 17% in EUR, and 36% in AFR).

Figure 1-2. Co-localization with a sQTL for FMO3 in liver

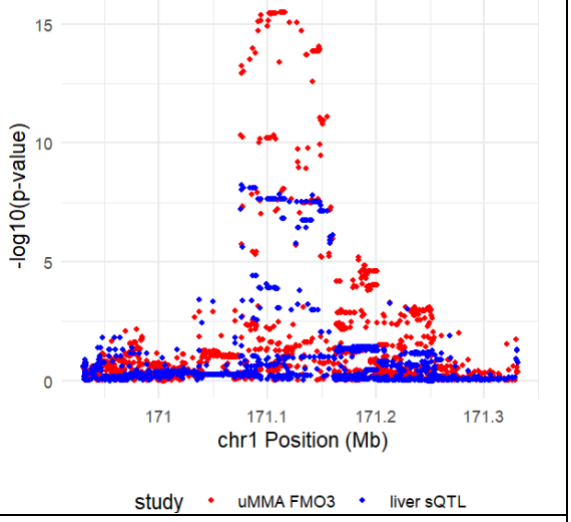


Figure 2. Co-localization with a sQTL (chr1:171110997:171114007) for *FMO3* in liver

1.3.2 GWAS of arsenic species measured in blood

A GWAS of blood arsenic species (bDMA%, bMMA%, and biAs%) among 976 individuals identified association signals in the *ASMT* and *FTCD* regions that are very similar to the association signals observed for urine arsenic metabolites observed in those regions (**Figure 3, Supplementary Figure 2**), in terms of both lead SNPs and direction of association. In addition, we observed two novel association signals, one in the FMO gene cluster (1q24.3) and one spanning the *GSTO1* and *GSTO2* genes at 10q25.1, in close proximity (<2 Mb) to the AS3MT association signal at 10q24.32 (**Figure 4**).

Figure 1-3. GWAS of Blood Arsenic

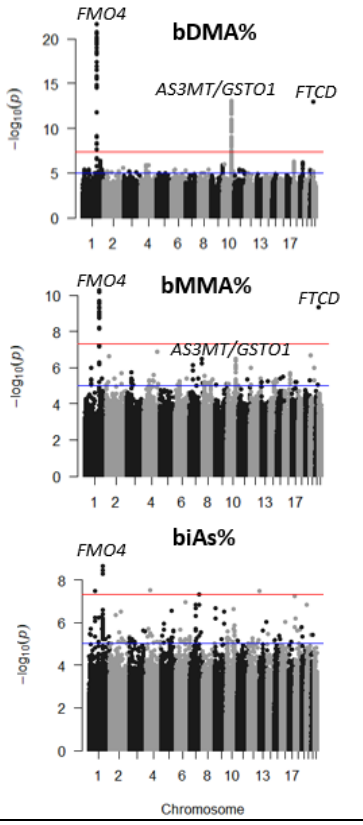


Figure 3. GWAS of blood arsenic species.

Figure 1-4. AS3MT and GSTO1 association signal on chromosome 10

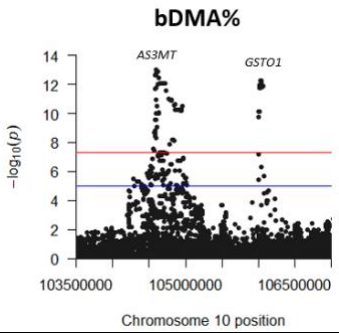


Figure 4. AS3MT association signal at chromosome 10

The FMO signal spans the *FMO4* and *TOP1P1* genes and is distinct from the association signal observed for urine arsenic species (which is centered on *FMO3*). The minor allele (C, MAF=45%) at lead SNP rs10912834 was associated with decreased blood DMA% (beta=-2.13; $P=2.3x10^{-22}$), increased blood MMA% (beta=1.35; $P=1.2x10^{-11}$), and increased blood iAs% (beta=0.78; $P=1.7x10^{-6}$). The signal at FMO4 observed for blood arsenic species was not observed for arsenic species in urine, and the signal at FMO3 observed for urine metabolites was not observed for blood metabolites (**Figure 5**). The MAF of lead SNP rs10912834 observed in HEALS (45%) was consistent with the MAF observed in 1KG BEB (46%) and SAS groups (45%). However, the MAF for rs10912834 varies somewhat across 1KG populations (30% in AMR, 41% in EAS, 35% in EUR, and 57% in AFR).

Figure 1-5. Association of SNPs in the FMO4 region with arsenic metabolism variables.

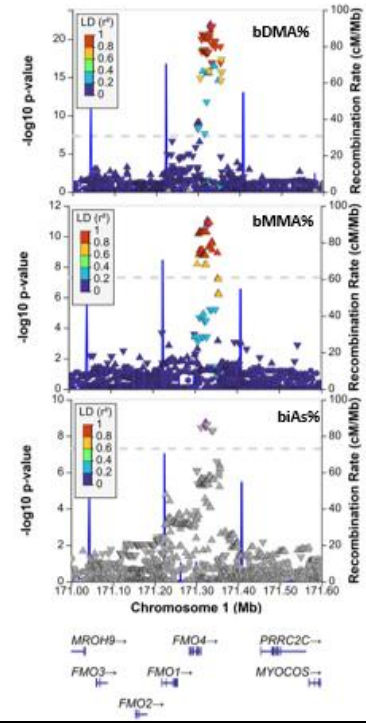


Figure 5. Association of SNPs in the *FMO4* region with arsenic metabolism variables.

The blood DMA% signal showed strong evidence of co-localization with a cis-eQTL for FMO4 present in at least 10 GTEx tissue types, including liver (PP4=0.81), pancreas (PP4=0.99) and artery-tibial (PP4=0.87) (Figure 6; **Supplementary Table 1**). The minor, MMA%-decreasing allele (C) was associated with increased expression of FMO4 in all of the GTEx tissues examined.

Figure 1-6. Co-localization with a cis-eQTL for FMO4 in pancreas

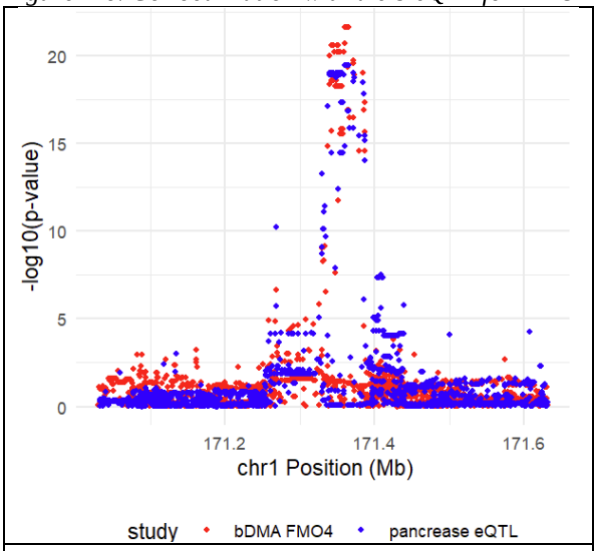


Figure 6. Co-localization with a cis-eQTL for *FMO4* in pancreas

The association signal observed at 10q25.1 spanned GSTO1 and GSTO2, with GSTO1 having a well-established role in arsenic metabolism, catalyzing the reduction of arsenic species (iAs^{V} to iAs^{III}, MMA^{V} to MMA^{III}, and DMA^{V} to DMA^{III}).[48, 49] The minor allele (T, MAF=10.3%) at lead SNP rs34521730 was associated decreased blood DMA% (beta =-2.70; $P=5.3x10^{-13}$), increased blood MMA% (beta=1.72; $P=3.5x10^{-7}$) and increased blood iAs% (beta=0.98, P=0.0004) (**Figure 7**). SNPs in this region did not show evidence of association with arsenic species measured in urine.

Figure 1-7. Association of SNPs in the GSTO1/GSTO2 region with As Metabolism variables

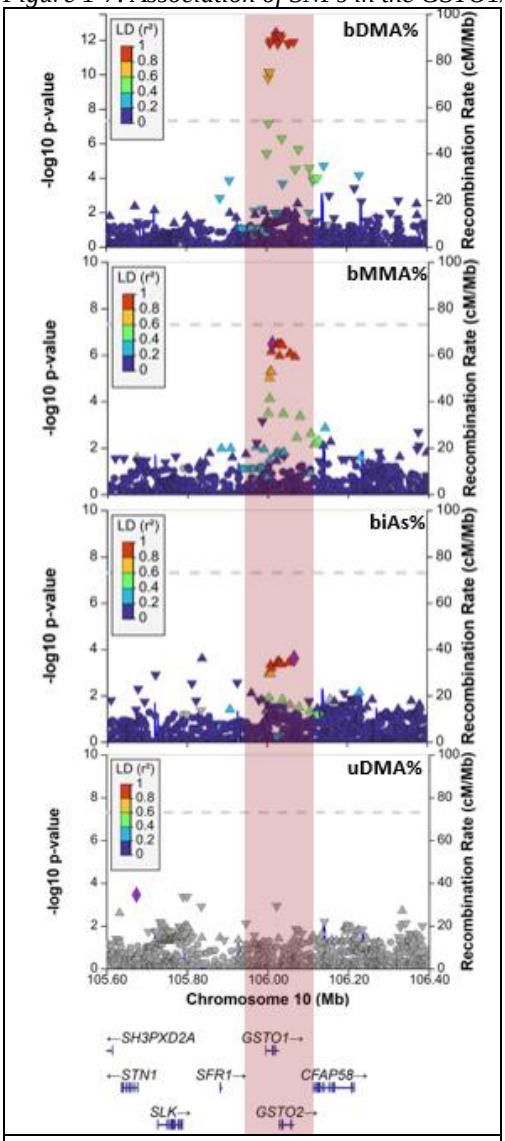


Figure 7. Association of SNPs in the GSTO1/GSTO2 region with arsenic metabolism variables.

Among the SNPs in the *GSTO1* region showing the strongest evidence of association was rs11509438 (DMA% P = 5.3×10^{-13}), a missense variant that codes for a GLU (E) to Lys (K) amino acid substitution. This variant has a CADD score of 0.46, SIFT score of 0.36/tolerated and PolyPhen score of 0.007/benign.

The *GSTO1* blood DMA% signal showed strong evidence of co-localization with a sQTL for GSTO1 in 53 GTEx tissues, including liver (PP4=0.99) and blood (PP4=0.99) (**Figure 8; Supplementary Table 1**). The minor, DMA%-decreasing allele (T) was associated with increased excision of the intron chr10:104263077:104266084, and decreased excision of an alternative intron chr10:104259798:104262979.

Figure 1-8.Co-localization of with sQTL for GSTO1 in Liver

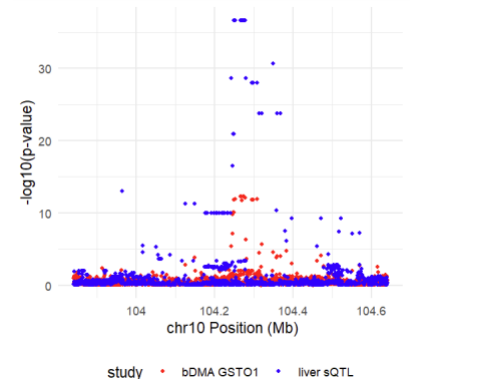


Figure 8. Co-localization of with sQTL(chr10:104263077:104266084) for *GSTO1* in Liver

In HEALS, the MAF of lead SNP rs34521730 is 10%, which is fairly consistent with the MAF observed in 1KG BEB (15%) and SAS groups (12%). The minor allele is less common across other 1KG populations (2% in AMR, 1% in EAS,3% in EUR, and 2% in AFR). We conducted a GWAS of blood total arsenic, but no clear associations were observed.

1.3.3 GWAS of arsenic-induced skin lesions

Using clinical data from genotyped participants from both HEALS and BEST (Bangladesh Vitamin E and Selenium Trial), we identified 3,438 participants with a diagnosis of arsenic-induced skin lesions (is the most common sign of arsenic toxicity) and 5,207 participants without history of a diagnosis. We conducted a GWAS of arsenic-induced skin lesion status, and

observed the strongest signal in the AS3MT region ($P=6.9x10^{-10}$; GC adjusted -Pvalue: $1.57x10^{-8}$, **Supplementary Figure 3**).

For *AS3MT* and *FTCD* SNPs that impact arsenic species in both urine and blood, the DMA%-decreasing alleles showed consistent evidence of association with increased skin lesion risk (Table 1). However, for the newly identified SNPs in the FMO and GSTO gene clusters, clear evidence of association with skin lesion risk was not observed.

Table 1-1. AME SNPs and skin lesion risk

Table 1. AME SNPs and skin lesion risk

	FMO3 rs12406572	**FMO4 rs10912834**	**GSTO1 rs34521730**	**AS3MT rs4919690**	**AS3MT rs11191492**	**AS3MT rs191177668**	**FTCD rs61735836**
Freq of low efficiency allele	0.93	0.45	0.10	0.11	0.87	0.01	0.07
Tissue type(s) effected	Urine only	Blood only	Blood only	Urine Blood	Urine Blood	Urine Blood	Urine Blood
DMA%	↓	↓	↓	↓	↓	↓	↓
Skin Lesion Association							
Odds Ratio	**0.95**	**1.06**	**0.88**	**1.3**	**1.1**	**2.0**	**1.3**
P-value	0.18	0.12	0.04	10^{-10}	0.02	10^{-5}	10^{-6}

3,438 skin lesion cases, 5207 controls

1.4 DISCUSSION

Using data from arsenic-exposed participants in Bangladesh, we performed GWAS of the relative abundance of three arsenic species, measured in both urine and blood: inorganic arsenic (iAs%), monomethylarsonic acid (MMA%), and dimethylarsinic acid (DMA%). We found that some genetic effects on these arsenic species are detectable in both blood and urine (*AS3MT* and *FTCD* SNPs), while others are detectable only in blood (*GSTO1, FMO4*) or only in urine (*FMO3*). The *AS3MT* and *FTCD* SNPs affecting arsenic metabolism show clear associations with risk of arsenic-induced skin lesions, while the newly identified metabolism-related variants (GSTO1, FMO3, and FMO4) do not.

We previously attempted to examine the impact of inherited variants on arsenic species measured in blood, providing evidence that FTCD and AS3MT SNPs had similar effects of arsenic species in blood as compared to urine arsenic species.[50] However, the sample size of our previous candidate SNP study was underpowered for GWAS of blood species, and therefore did not identify the FMO and GSTO regions reported here.

Our observation that genetic effects on arsenic species can be detectable in blood, by apparently absent in urine (and vice versa), is somewhat unexpected given our prior findings that (1) AS3MT and FTCD SNPs have similar effects on metabolites in blood compared to urine and (2) arsenic species percentages (e.g., DMA%) measured in blood are positively correlated with the same metabolite percentage measured in urine. [50] While these prior findings suggest that the arsenic species composition of urine should reflect that of the blood that is being filtered by the kidney, our new findings point to complexities in arsenic metabolism, distribution, and/or excretion that we do not yet fully understand. Such complexities could involve gene/enzyme

functions that vary by cell or tissue type, important variability in the valence states of arsenic species that we are unable to measure, and/or alternative pathways and of metabolism and elimination (e.g., gut). Further research is needed to elucidate the precise mechanisms underlying these differential associations.

The association signal observed for urine species at FMO3 is unique because the association is more pronounced for MMA% compared to DMA% (and undetectable for iAs%). For all other regions identified (AS3MT, FTCD, FMO4, and GSTO1), the SNPs' associations are most prominent for DMA%, suggesting a different toxicokinetic impact of the FMO3 causal variant compared to the other regions.

FMOs are known to be involved in the oxygenation of xenobiotics, they have not previously been reported to have a role in arsenic metabolism. FMO enzymes are known primarily for oxidation of xenobiotic substrates. While oxidation is not a key step in the Challenger pathway, oxidation by FMOs could potentially play a role in reversing the GSTO1-catalyzed reduction of arsenic species. Alternative pathways of arsenic metabolism have been proposed in which trivalent arsenic species are directly methylated, without oxidation. The resulting trivalent methylated species can then undergo oxidation to form pentavalent species, but this step is a secondary process and not required for methylation (under the alternative pathway). This alternative pathway potentially provides a role for FMOs in the oxidation step.[51, 52] However, additional research is needed to understand the involvement of FMO enzymes in the metabolism of arsenic.

SNPs in FMO genes have been reported in GWAS to associated with for blood cell traits,[53] metabolomics phenotypes[54], and hormonal phenotypes.[55] For example, one of the FMO SNPs (rs12406572) has been reported as a metabolite QTL for methylcysteine.[53] Mutations in

FMO3 cause trimethylaminuria, also known as "fish odor syndrome", a condition in which a defective FMO3 enzyme causes accumulation of trimethylamine, which results in a distinctive odor resembling rotten fish.[56]

FMO2 has recently been shown to play a role in one-carbon metabolism (OCM) in C.*elegans*, [57] an essential metabolic pathway that provides one-carbon units for methylation regions encompassing the folate and methionine cycles. This suggests that FMOs could potentially influence AME through the OCM pathway rather than through biotransformation of arsenic species.

The association identified for SNPs in the 10q25.1 region are likely to affect the function of GSTO1, a gene known to reduce pentavalent arsenic species to trivalent forms. Previous epidemiological studies have linked GSTO SNPs to arsenic-related phenotypes[58, 59] providing evidence of their involvement in arsenic toxicity and metabolism Additionally, a separate study has provided insights into the distribution and frequencies of GST variants among different Ecuadorian populations and their relationship to global populations, suggesting that certain *GSTO1* variants may be under selective pressure, particularly in the context of arsenic metabolism susceptibility.[60] However, the present study is the first to demonstrate an association between human genetic variation in this region and arsenic metabolism efficiency.

Previously identified SNPs in the AS3MT and FTCD regions show consistent association of the DMA%-decreasing allele with elevated risk of arsenic-related skin lesions. This finding supports the hypothesis that genetic variants that influence the methylation of arsenic, and hence the elimination and internal dose of arsenic, will have downstream impacts on risk of arsenic-related health conditions. However, newly identified SNPs in the FMO and GSTO regions did not show clear associations with arsenic induced skin lesions. This lack of associations could be

due to power limitations, but it is also possible that SNPs influencing the reduction (or oxidation) of arsenic species, as opposed to methylation, may influence the distribution pentavalent versus (the more toxic) trivalent species in human tissues. While we cannot capture such effects in this study, they could have implications for toxicity risk, adding a layer of complexity to our underlying hypothesis that increasing DMA production should always decrease toxicity risk.

For colocalization analyses, we leveraged eQTL and sQTL data from GTEx, a study of tissue donors largely of European ancestry. While the ancestry (and associated LD patterns) of GTEx are not well-matched to HEALS participants of Bangladeshi ancestry, our colocalization analyses produced strong posteriors, despite the LD mismatch.

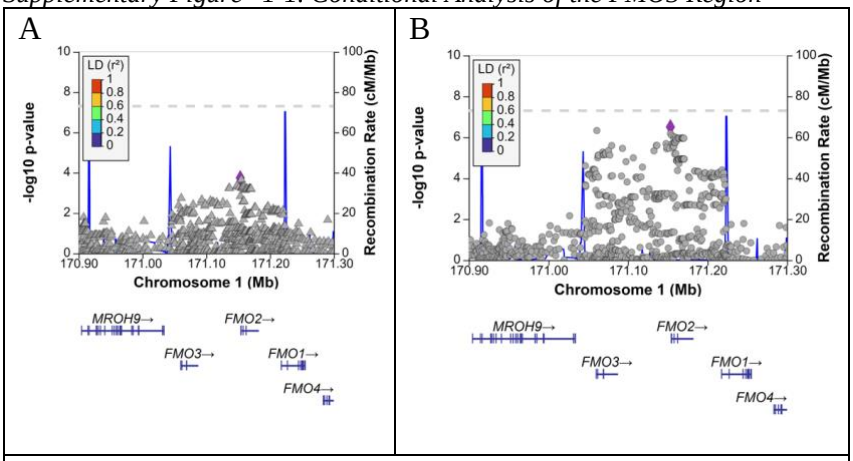
Next steps for this research include replication of the reported associations in other populations with arsenic exposure and evaluating our metabolism related SNPs for association with other arsenic-related health outcomes. Additional research is needed to characterize the molecular mechanisms by which the identified variants impact gene function, their relevant cellular contexts, and their roles in pathways involved in arsenic metabolism.

1.5 CONCLUSION

In conclusion, our study investigated the genetic effects on arsenic species in blood and urine using GWAS in a population exposed to arsenic in Bangladesh. We identified specific genetic variants, such as *AS3MT* and *FTCD* SNPs, that were associated with arsenic species in both blood and urine. However, we also found variants, including *GSTO1, FMO3,* and *FMO4*, that showed associations only in either blood or urine. These findings suggest complexities in arsenic metabolism and elimination that are not fully understood. Furthermore, we observed differential associations between genetic variants and arsenic species, with FMO3 showing a

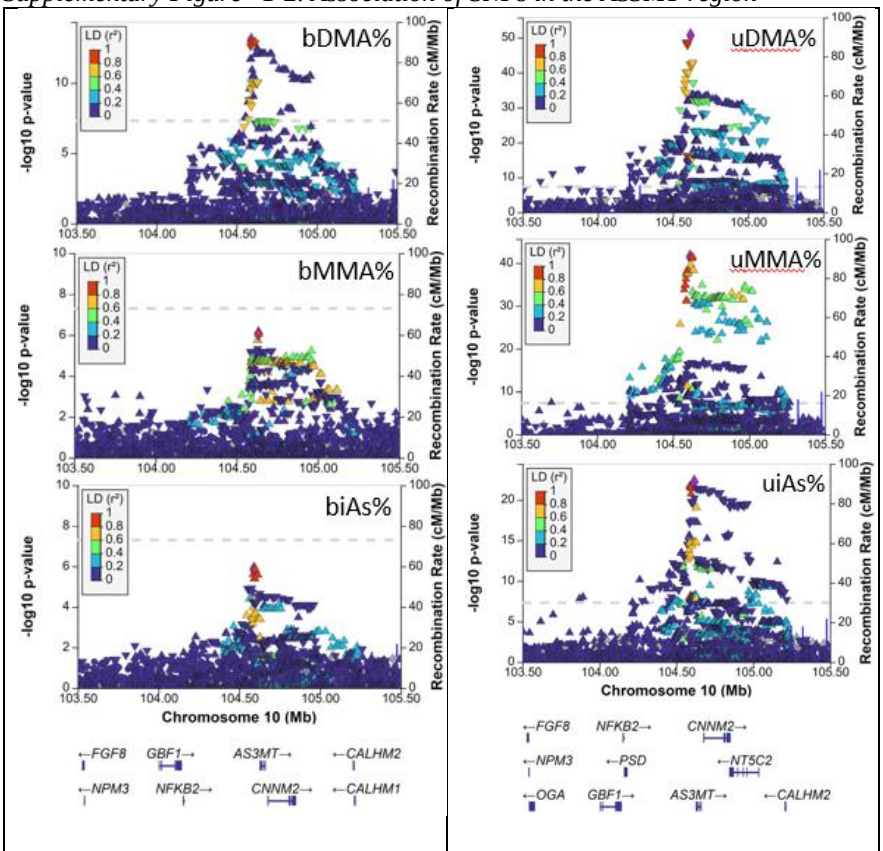
pronounced association with monomethylarsonic acid (MMA%) compared to dimethylarsinic acid (DMA%). The involvement of FMO enzymes in arsenic metabolism is intriguing and warrants further investigation. Additionally, SNPs in the 10q25.1 region likely affect the function of GSTO1, a gene known to reduce pentavalent arsenic species. Our study provides novel insights into the genetic variations underlying arsenic metabolism, but further research is needed to validate these associations in other populations and elucidate the molecular mechanisms involved.

Supplementary Figure 1-1. Conditional Analysis of the FMO3 Region



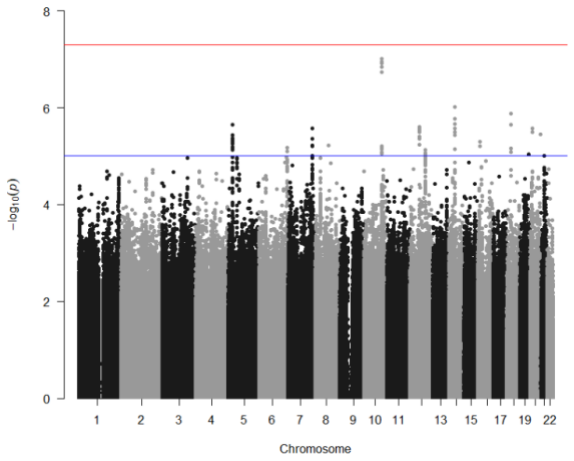
Supplementary Figure 1. Conditional Analysis of the FMO3 Region. A) uDMA% adjusted for lead SNP rs12406572. B) uMMA% adjusted for lead SNP rs12406572.

Supplementary Figure 1-2. Association of SNPs in the AS3MT region



Supplementary Figure 2. Association of SNPs in the AS3MT region with A) bDMA%, bMMA, and bias; B) uDMA%, uMMA, and uiAs%.

Supplementary Figure 1-3. Arsenic induced skin lesions GWAS



Supplementary Figure 3. Arsenic induced skin lesions GWAS

Supplementary Table 1-1. Colocalization

Supplementary Table 1. Colocalization

biospecimen	Lead SNP (p)	Type	Intron excision (hg38)	Beta	Pvalue	Tissue (n)	Gene Region	H0	H1	H2	H3	H4
blood DMA	rs34521730 (5.3E-13)	sQTL	chr10:104263077:104266084:clu_7798	-2.68	$2.1x10^{-37}$	Liver (208)	GSTO1	6.38E-33	6.39E-27	1.15E-08	0.0106	0.9890
blood DMA	rs34521730 (5.3E-13)	sQTL	chr10:104259798:104262979:clu_9220	2.44	$3.8 x10^{-85}$	Whole Blood (670)	GSTO1	2.51E-88	2.52E-82	1.04E-08	9.45E-03	0.9910
blood DMA	rs34521730 (5.3E-13)	sQTL	chr10:104259798:104262979:clu_9659	2.9	$6.9x10^{-109}$	Cells (483)	GSTO1	9.73E-165	9.74E-159	1.21E-08	0.0112	0.9890
blood DMA	rs10912834 (2.26E-22)	eQTL	Not Applicable	0.47	$7.1x10^{-22}$	Liver (208)	FMO4	3.89E-37	5.57E-21	1.33E-17	0.19	0.81
blood DMA	rs10912834 (2.26E-22)	eQTL	Not Applicable	0.59	$6.9x10^{-63}$	Artery Tibial (584)	FMO4	7.47E-94	1.07E-77	9.44E-18	0.13	0.87
blood DMA	rs10912834 (2.26E-22)	eQTL	Not Applicable	0.58	$3.4x10^{-20}$	Pancreas (305)	FMO4	6.75E-34	9.65E-18	1.04E-18	0.01	0.99
Urine MMA	rs12406572 (3.13E-16)	sQTL	chr1:171110997:171114007:clu_36292	-0.64	$5.8x10^{-9}$	Liver (208)	FMO3	7.71E-15	1.52E-04	2.92E-12	0.0568	0.9430
Urine MMA	rs12406572 (3.13E-16)	sQTL	chr1:171092790:171107675:clu_55260	1.54	$1.4x10^{-150}$	Adipose Sub (581)	FMO3	0.00	1.22e-315	1.13E-12	2.13E-02	0.9787
Urine MMA	rs12406572 (3.13E-16)	sQTL	chr1:171110997:171116208:clu_58733	0.95	8.89E-49	Lung (515)	FMO3	3.78E-61	7.48E-51	1.11E-12	2.09E-02	0.9791

Chapter 2 RETURNING PERSONAL GENETIC INFORMATION ON SUSCEPTIBILITY TO ARSENIC TOXICITY TO RESEARCH PARTICIPANTS IN BANGLADESH

2.1 INTRODUCTION

In human genetic studies, it is now common for researchers to consider returning personal genetic results to participants who wish to receive it.[61-64] It has been suggested that providing participants with their genetic information is one way researchers can demonstrate respect for participants and enhance their engagement in research.[62] In addition, genetic information has the potential to change individuals' perceived disease risks and motivate changes in lifestyle and/or health care utilization.[64, 65]

Personal genetic information could also motivate individuals to reduce their exposure to environment chemicals to which they are susceptible.[66] In the Health Effects of Arsenic Longitudinal Study (HEALS), a cohort in Bangladesh with substantial exposure to arsenic through drinking water, participants previously reported a strong interest in receiving genetic information related to their susceptibility to the effects of arsenic.[67] Even among participants who are not particularly concerned about the health effects of arsenic, there was substantial interest in receiving information on genetic susceptibility to arsenic toxicities[67], suggesting that HEALS participants with long-term high arsenic exposure may be more receptive to behavior changes that reduce exposure if made aware of their genetic risk.

Inorganic arsenic (iAs) is a carcinogen, and exposure to high levels of iAs (>10 µg/L) affects approximately 150 million individuals worldwide,[68] including >57 million in Bangladesh.[3, 4] Chronic exposure to high levels of iAs in drinking water and soil affects over 70

countries[69-71], increasing the risk for a wide array of health problems related to arsenic exposure, including cancer, cardiovascular diseases, and skin lesions.[72, 73]

There is inter-individual variation in arsenic metabolism efficiency (AME),[4, 20, 25, 28] and this variability impacts internal dose of arsenic and toxicity risk. Multiple common variants near the *AS3MT* gene impact AME, as does a genetic variant in the formiminotransferse cyclodeaminase (*FTCD*) gene. In the HEALS, *FTCD* and *AS3MT* variants together explain ~10% of the variation in AME and have clear effects on toxicity risk (i.e. arsenic-induced skin lesions).[19]

In this study, we analyze the impact of returning genetic results on arsenic susceptibility to research participants in a rural area where a substantial percentage of drinking wells are naturally contaminated with arsenic. These results are considered "actionable", as participants can take actions to decrease their exposure (e.g., well-switching[74]) that could be enabled by knowledge of their genetic data.[66] Data on genetic variation in *AS3MT* and *FTCD* allows us to identify individuals who are inefficient (i.e., slow) arsenic metabolizers (as opposed to high efficiency metabolizers) and implement an intervention to return personal genetic information on susceptibility to arsenic toxicity to participants in rural Bangladesh. To assess arsenic exposure and the effects of the intervention urine samples were collected at baseline and at a 6-month follow-up.

2.2 METHODS

2.2.1 Overview of Study Design

We selected intervention groups based on genotype (i.e., inefficient and efficient arsenic metabolizers, respectively) and selected a control group randomly from genotyped participants

not receiving the intervention. At initial contact (Time 1: June 2021-December 2021), UChicago Research Bangladesh (URB; an international research institute) trained field staff administered questionnaires and obtained urine samples from all participants (**Figure 1**). The field staff were trained by senior research members. A one-on-one informational intervention was provided to all participants, reminding them of the effects of arsenic exposure and strategies to reduce their exposure (e.g. well-switching)[74]. The intervention groups were also provided information on metabolism efficiency (i.e., their genetic results) via a factsheet. Two months after baseline (Time 2: August 2021-February 2022), the intervention group received a reminder of their genetic results and informational intervention and the control group received a reminder of the informational intervention. Six months after the intervention (Time 3: December 2021- June 2022), urine was collected for all participants, follow-up questionnaires were administered, and the control group was provided their genetic results regarding AME (if they wished to receive it).

The study protocol was approved by the University of Chicago IRB and the ethics committee of the Bangladesh Medical Research Council (BMRC). All participants gave written informed consent before initiation of study activities.

Figure 2-1. Overview of the design for the return of genetic results intervention study

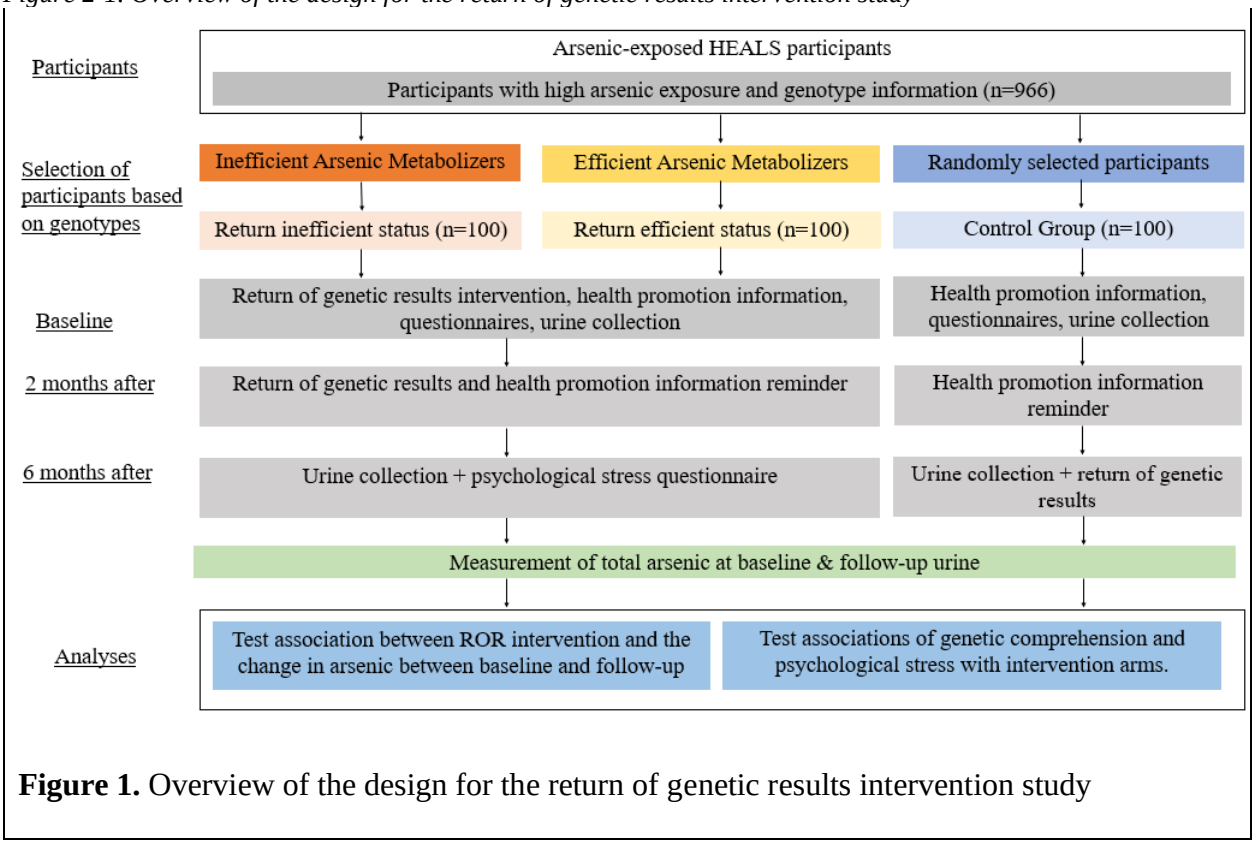


Figure 1. Overview of the design for the return of genetic results intervention study

2.2.2 Theoretical Framework

We were guided by the Health Belief model[75, 76] in designing the study. The five key beliefs postulated in the model are (1) perceived susceptibility to a condition, (2) perceived severity of a condition, (3) perceived benefits of an action, (4) perceived barriers to completing an action, and (5) perceived self-efficacy of completing an action. This model underlies the design of our study and the return of genetic results intervention.

Returning genetic results relies on the assumption that genetic knowledge will motivate behavioral change to reduce risk of disease or improve health.[77] We hypothesize that knowledge of one's genetic susceptibility to arsenic toxicity will impact participants' perceived risk (with the understanding that age, sex, education, genetic comprehension, and other factors may also

impact this perception). This perceived risk in turn will impact health behaviors (e.g., well-switching) that can reduce exposure, leading to lower arsenic-related health risks (**Figure 2**). Health behavior change may be impacted by additional factors such as cultural beliefs and access to health information.

Figure 2-2. Theoretical framework showing the hypothesized impact of the return of genetic results intervention on arsenic toxicity risk.

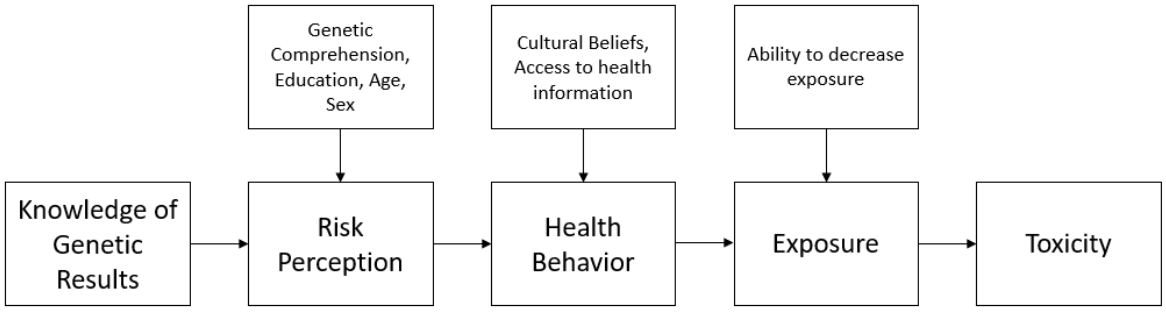


Figure 2. Theoretical framework showing the hypothesized impact of the return of genetic results intervention on arsenic toxicity risk.

2.2.3 Study Participants

Participants for this study were recruited from The Health Effects of Arsenic Longitudinal Study (HEALS).[34] HEALS is a prospective longitudinal study of health outcomes associated with arsenic exposure through drinking water among adults in Araihazar, Bangladesh, a rural area with substantial exposure to arsenic through naturally contaminated drinking water from local wells. HEALS began in 2000 and is comprised of >20,000 active adult participants (followed over 15-20 years to ascertain health outcomes), of which 5,905 have existing genome-wide SNP data.[19, 20, 27, 29, 50, 78] Trained study physicians conducted in-person interviews, clinical evaluations, and urine collection (every 2 to 4 years since 2000). Eligible participants for this study were HEALS cohort members (age 18-60 at the time of recruitment to the present study)

with (1) high urine arsenic levels (≥ 150 µg/g creatinine) based on their last measured follow-up urine data and (2) existing genetic data on *AS3MT* and *FTCD* variants that could be used to classify participants according to their AME. HEALS participants missing urine arsenic measurements at either baseline or the last measured follow-up were not eligible. One hundred participants had their last measured follow-up in 2011, 40 in 2017 and 160 in 2018.

2.2.4 Genotyping and Quality Control

A subset of HEALS participants (n = 5,905) were genotyped previously using Illumina arrays (either HumanCyto12 300K or Infinium multiethnic EUR/EAS/SAS 1.4M array) at research laboratories of UChicago. For both arrays, we removed non-rs SNPs, SNPs with a call rate of <90%, monomorphic SNPs, and samples with a call rate <90%. The Michigan Imputation Server was used to conduct genotype imputation using the Haplotype Reference Consortium (HRC).[40] Only high-quality imputed biallelic SNPs (imputation $r^2 > 0.3$) and SNPs with minor allele frequency >0.005 were retained. From this dataset, we extracted data for our four SNPs of interest (rs4949690, rs191177668, rs11191492 in the *AS3MT* region and rs61735836 in *FTCD)* previously shown to be associated with AME and risk of arsenic-induced skin lesions.[19, 20, 27, 50]

2.2.5 Genetic Classification of efficient vs. inefficient metabolizers

We created a polygenic risk score using the *AS3MT* and *FTCD* variants to classify participants as efficient or inefficient metabolizers, selecting individuals at the extremes of the score. The PRS was constructed by summing the count of high efficiency alleles across all four SNPs, weighing the allele count for each SNP by the SNP's effect size on AME. Our PRS includes 4 risk variants (rs4949690, rs191177668, rs11191492 in the *AS3MT* region and rs61735836 in *FTCD*). Specifically, for individual i,

$$PRS_i = \sum_{m=1}^{M} w_m g_{im}$$

where g_{im} is the genotype dosage of the low efficiency allele for individual i for variant m and w_m is the variant-specific weight, a beta coefficient estimated from linear regression in our prior GWAS. M is the total number of variants included (M=4).

We created a list of eligible participants for the URB field team to recruit from that consisted of 293 eligible for the inefficient group, 300 eligible for the efficient group and 373 eligible for the control group (**Figure 3**). Due to limited numbers of inefficient and efficient arsenic metabolizers, our control group consisted primarily of normal/average metabolizers.

Figure 2-3. Distribution of polygenic risk score.

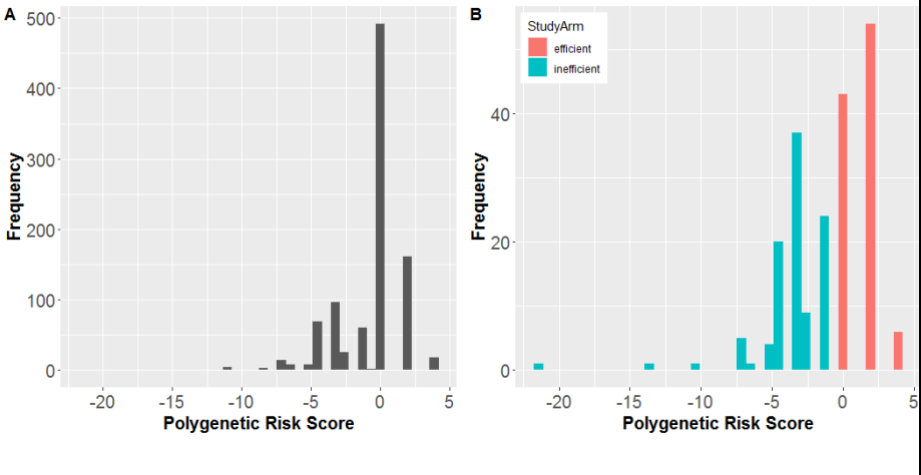


Figure 3. Distribution of polygenic risk score. A) All eligible HEALS participants (n=966) B) Participants recruited in the intervention arms of the study (n=206).

2.2.6 Return of Genetic Results Intervention

All participants received an informational intervention, in which a URB team member explained the potential health effects of arsenic exposure and provided them strategies for

reducing their exposure, such as well switching, using supporting visual aids (**Supplementary File 1).** The intervention groups received information regarding their genetic susceptibility to arsenic toxicity (based on genetic variants that influence arsenic metabolism efficiency). They received this information through a factsheet appropriate for a lay audience (**Supplementary File 2**), communicated with the help of URB team members. The factsheet contained information and described the variability among individuals with respect to the efficiency with which arsenic is removed from the body, due to inherited differences in genes that affect arsenic metabolism. The factsheet also informed the participant whether they had been identified as either a slow or fast metabolizer of arsenic based on their genes. The control group did not receive information regarding their genetic results that informed them of their arsenic metabolism efficiency until the end of the study.

All the genetic results and accompanying information was provided to participants by a member of the URB team (in person) who was able to explain the factsheet and their genetic results. The URB staff have worked with this community for many years. Participants had the opportunity to direct questions regarding their genetic results to URB staff at the time their results were provided, and a study physician was available to address additional concerns of the participant.

2.2.7 Questionnaires

We administered a modified version of our previous questionnaire used in HEALS called the Return of Results (Genetic) Questionnaire[67] at baseline to all participants in Bangladesh. This questionnaire collected information on demographics, current perceived arsenic exposure status, and attitudes towards receiving genetic results. Past data has shown that 96% of wells with high arsenic levels are located within 100m of at least one low arsenic well, [74, 79, 80] suggesting that the

vast majority of households have the ability to switch to a lower arsenic well. To assess participants' expectations regarding their ability to reduce their arsenic exposure, a question regarding this topic was administered (Supplementary Table 1, Question 4).

Both intervention groups also received a genetic comprehension questionnaire. We measured genetic comprehension using a modified version of the Measure of Genetic Comprehension[81, 82] questionnaire, tailored to our study population, to determine if low genetic comprehension is a potential barrier for participants to understand and benefit from genetic information. This questionnaire was administered in person to participants by research staff who followed structured protocols.

Participants in the intervention arms were also given a questionnaire 6 months after the intervention to measure any psychological stress due to receiving genetic results. We used an altered version of the Feelings About genomiC Testing Results (FACToR) questionnaire[83], tailored to our study population. FACToR was designed to measure the psychological impact of receiving genomic test results. Participants who experience higher levels of stress due to receiving geneticresults were offered additional consultations by the research staff. This questionnaire was followed by a short survey, asking participants to disclose any arsenic-related behavioral changes related to receiving their genetic results. Questions assessed the impact of genetic results on participants' motivation to switch their current water source in an attempt to reduce their arsenic exposure, and participants' reasons for not switching.

2.2.8 Arsenic measurements

Total urinary arsenic concentration was measured by the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) using graphite furnace atomic absorption

spectrometry with a detection limit of 2 µg/L.[84] Urinary creatinine concentration was measured using the Randox Jaffe Creatinine Assay, a colorimetric technique based on the Jaffe reaction.[37] A creatinine-adjusted total arsenic concentration (µg/g creatinine) was obtained by dividing the total urinary arsenic concentration (µg/L) by urinary creatinine concentration (Mg/dL) and multiplying this by 100.

2.2.9 Statistical Analysis

We used three different regression analyses[85, 86] to determine if the change in exposure (from baseline to 6 months after the intervention) differs across the three study arms (return inefficient status, return efficient status, and control). For equations 1 and equation 2, fifty-two outliers were detected and removed using interquartile range (IQR) technique.[87] For equation 3 is a robust regression[88] that reduces the impact of outliers by downweighing the influence of outliers by assigning weights to each datapoint based on their influence. Points that are closer to the majority of the data are assigned higher weights, while outliers are given lower weights or even downweighed to zero.

eq 1: $\mathrm{UrineAsCr}_{\mathrm{Time\,2}} - \mathrm{UrineAsCr}_{\mathrm{Time1}} = \beta_1 \mathrm{Treatment\ Arm} + \beta_2 \mathrm{UrineAsCr}_{\mathrm{Time1}} + \beta_3 \mathrm{Age} + \beta_4 \mathrm{Sex} + \mathrm{error}$

eq 2: $\frac{\mathrm{UrineAsCr}_{\mathrm{Time\,2}} - \mathrm{UrineAsCr}_{\mathrm{Time1}}}{\mathrm{UrineAsCr}_{\mathrm{Time1}}} = \beta_1 \mathrm{Treatment\ Arm} + \beta_2\ \mathrm{Age} + \beta_3 \mathrm{Sex} + \mathrm{error}$

eq 3: Same as eq.1 (robust regression)

2.3 RESULTS

2.3.1 Participant characteristics

There were 309 participants recruited for this study (103 efficient metabolizers, 103 inefficient metabolizers, and 103 controls, **Table 1**). The average age was 50 years, and most participants were female (72.2%), with females being slightly younger than males, consistent

with the larger HEALS cohort[89]. Over half of the participants had no formal education (59.5%). The average baseline creatinine-adjusted urine arsenic (µg/g) was somewhat higher in the control group (128.4 µg/g) compared to the inefficient (121.3 µg/g) and efficient groups (115.7 µg/g), but these differences were not statistically significant (Chi-square P=0.75), reflecting the quasi-randomization of participants by genotype and random selection of controls.

Table 2-1.Baseline characteristics of HEALS participants recruited to the return of genetic results intervention study
Table 1. Baseline characteristics of HEALS participants recruited to the return of genetic results intervention study

	Overall	Control	Efficient	Inefficient	P-value*
n	309	103	103	103	
Age in years, mean (SD)	50.1 (6.8)	50.8 (7.2)	49.6 (6.7)	49.9 (6.3)	0.42
Age in years, n (%)					
34-40	25 (8.1)	7 (6.8)	11 (10.7)	7 (6.8)	
41-50	140 (45.3)	45 (43.7)	44 (42.7)	51 (49.5)	0.54
51-60	139 (45.0)	48 (46.6)	48 (46.6)	43 (41.7)	
61-78	5 (1.6)	3 (2.9)	0 (0.0)	2 (1.9)	
Sex (%)					
Females, n (%)	223 (72.2)	74 (71.8)	77 (74.8)	72 (69.9)	0.74
Age for males, mean (SD)	53.1 (6.6)	54.6 (7.3)	53.3 (6.1)	51.5 (6.3)	0.19
Age for females, mean (SD)	48.9 (6.4)	49.3 (6.7)	48.3 (6.5)	49.2 (6.2)	0.59
Years of formal education (%)					
0	184 (59.5)	61 (59.2)	57 (55.3)	66 (64.1)	
1-4	28 (9.1)	11 (10.7)	10 (9.7)	7 (6.8)	0.79
5-7	59 (19.1)	19 (18.4)	20 (19.4)	20 (19.4)	
8-11	38 (12.3)	12 (11.7)	16 (15.5)	10 (9.7)	
Baseline urinary arsenic adjusted for creatinine (µg/g), mean (SD)	121.8 (119.8)	128.4 (140.5)	115.7 (106.7)	121.3 (110.1)	0.75

Values are n (%)
*Chi-square test are used categorial variables, t-test for continuous variables

2.3.2 Return of Genetic Results Recruitment survey

Responses to the baseline survey assessing attitudes towards return of genetic results is described in **Supplementary Table 1**. Almost all participants were concerned about the health effects of arsenic-contaminated drinking water (97%; Question 1) and interested in receiving information on genetic susceptibility (>99%; Question 2). Overall, ~13% of participants believed

their water source to be free of arsenic (Question 3), and this percentage varied slightly across the three study arms. Notably, ~90% of the participants believed that they could take steps to further reduce their arsenic exposure (Question 4). Across all study arms, nearly all participants felt comfortable in sharing their genetic information with family members (Question 6).

2.3.3 Genetic Comprehension Survey

The results of the Measure of Genetic Comprehension Survey are provided in **Supplementary Table 2**. Among all participants, 77% answered all the comprehension questions correctly (**Figure 4** and **Supplementary Table 2)**. When assessing differences in genetic comprehension by study arm, there were no differences observed.

Figure 2-4. Genetic comprehension survey scores by study arm

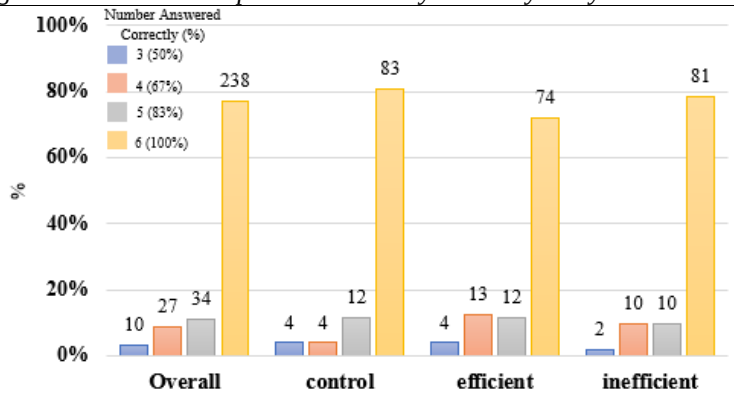


Figure 4. Genetic comprehension survey scores by study arm. Participants received one point for each of the six question that was answered correctly. Participants with a score of 6 answered all questions correctly.

2.3.4 Measured Urine Arsenic Levels

Urine arsenic levels adjusted for creatinine measured at baseline and the 6-month follow-up are shown in **Figure 5**. At baseline, average urine arsenic levels were 128.4, 115.7 and 121.3 µg/g for the control, efficient and inefficient group, respectively, while at the 6-month follow-up, the mean urine arsenic level was 76.9, 89.1, and 79.6 µg/g for the control, efficient and

inefficient group, respectively. Compared to baseline urine arsenic, all three study arms experienced a decrease in urine arsenic levels (**Figure 5**). During the follow-up period, 4 (3.9%) participants within the efficient status and 1 (0.3%) participant within the inefficient group were lost to follow-up.

Figure 2-5. Urine arsenic levels at baseline and at 6 months follow-up

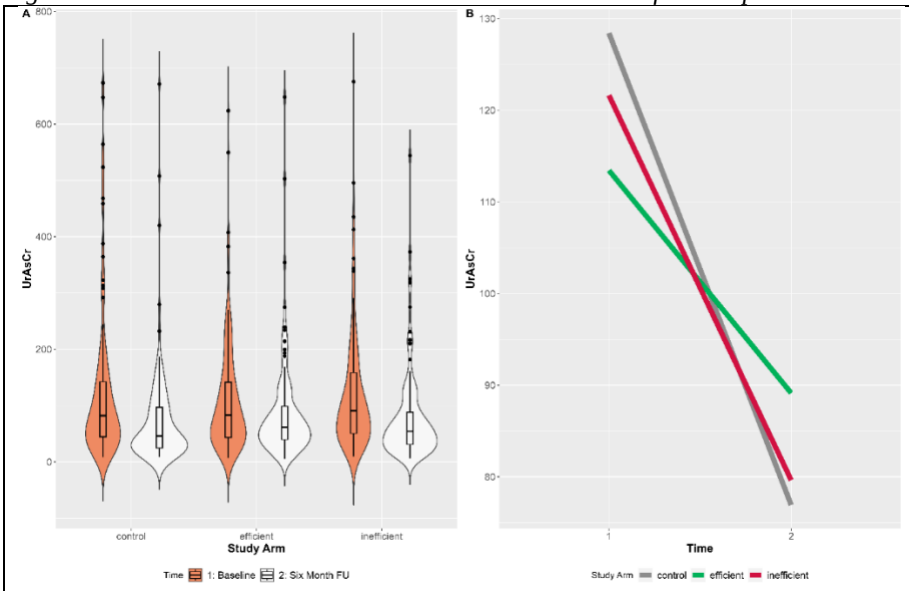


Figure 5. Violin plot of urine arsenic levels at baseline and at 6-month follow-up by study arm (A). The Mean UrAsCr by study arm across time (B).

We performed 3 different regression analysis to assess differences in the change in urine arsenic across the three study arms (**Table 2**). For Model 1 and Model 2 fifty-two outliers were removed using the interquartile range (IQR) method. In model 1, the beta coefficient is interpreted as the group difference in the change between urine arsenic measurements at baseline and follow-up. For Model 1, neither the efficient group (p=0.44) nor the inefficient arm (p=0.96) was different from the control arm in terms of the change in arsenic from baseline to follow-up. In model 2, the beta coefficient is interpreted as the relative difference in follow-up urine arsenic levels (adjusted for baseline levels). In model 2, neither the efficient group (p=0.57) nor the inefficient group (p=0.79) differed from the control arm. Model 3 used robust regression which

is less sensitive to outliers. In model 3, there were no differences observed for either the efficient group (p=0.18) or the inefficient group (p=0.87) when compared to the control group.

Table 2-2. Regression analysis of urine arsenic measurements

Table 2. Regression analysis[1] of urine arsenic[2] measurements

	"Group Difference" Model 1 (n=252)	"Relative Difference" Model 2 (n=252)	Robust Regression Model 3 (n=304)
	Beta (P-value)	Beta (P-value)	Beta (P-value)
Efficient (Ref: control)	3.4 (0.44)	0.1 (0.57)	11.3 (0.18
Inefficient (Ref: control)	0.3 (0.96)	-0.05 (0.79)	4.18 (0.87)

Group Difference Model 1: $\text{UrineAsCr}_{\text{Time 2}} - \text{UrineAsCr}_{\text{Time1}} = \beta_1 \text{Treatment Arm} + \beta_2 \text{UrineAsCr}_{\text{Time1}} + \beta_3 \text{Age} + \beta_4 \text{Sex}$, linear regression

Relative Difference Model 2: $\frac{\text{UrineAsCr}_{\text{Time 2}} - \text{UrineAsCr}_{\text{Time1}}}{\text{UrineAsCr}_{\text{Time1}}} = \beta_1 \text{Treatment Arm} + \beta_2 \text{ Age} + \beta_3 \text{Sex}$, linear regression

Robust Model: Same equation as model 1, using robust regression which reduces the impact of outliers by downweighing the influence of outliers by assigning weights to each datapoint based on their influence.

[1]Adjusted for age and sex

[2] creatinine-adjusted

We identified, 29 spouse-pairs, or 58 participants, who live in the same household (**Supplementary Table 3**), however, only 22 of these participants, 11 spouse-pairs, (7.1% of our study population) had a mixed household with a participant from the control group. There was only 1 first-degree relationship pair among our participants, both of which were in the control group. A sensitivity analysis was conducted removing the 29 spouse-pairs from the analysis, and results were similar to the primary analysis.

2.3.5 Self-Reported Well-Switching

At the 6-month follow-up visit, 100% of the participants across both intervention arms stated that receiving their genetic results motivated them to at attempt to reduce their exposure to arsenic (**Table 3**). However, the inefficient group had larger percentage of participants (88.2%) that self-reported switching wells in the past 6 months in the attempt to reduce exposure compared to the efficient (37.6%) and the control group (42.7%) (P <0.001). Among participants

who did not self-report switching wells (across all arms combined), the majority found it was too difficult to switch (69.9%), some found access to wells in their community not feasible (23.3%) and a few stated that they already drank from an arsenic-free water supply (6.8%). However, when assessing self-reported water switching and observed changes in urine arsenic, self-reported switching did not show a clear association with change in urine arsenic (from baseline to follow-up) within any of the three arms (efficient pvalue=0.65; inefficient pvalue=0.47) (**Supplementary File 3**).

Table 2-3. Return of genetic results and well-switching
Table 3. Return of genetic results and well-switching

	Control	Efficient	Inefficient	p-value
In the last 6 months, did receiving genetic results motivate you to change your water source to lower your arsenic exposure? (%)				
Yes	NA	101 (100.0)	102 (100.0)	NA
Switched Water Source (%)				
Yes	44 (42.7)	38 (37.6)	90 (88.2)	<0.001
No	59 (57.3)	63 (62.4)	12 (11.8)	
Why Not Switched?				
Not Concerned	0 (0)	0 (0)	0 (0)	0.874
Too difficult to switch	39 (66.1)	45 (72.6)	9 (75.0)	
Access to wells in my community is not feasible (SES factors)	15 (25.4)	14 (22.6)	2 (16.7)	
Other	5 (8.5)	3 (4.8)	1 (8.3)	

2.3.6 FACToR Questionnaire

In the two intervention arms, we assessed participants' feelings at six-month follow-up regarding receiving their genetic information (**Supplementary Table 4**). Participants in the inefficient arm reported more anxiousness and nervousness regarding their genetic results compared to those in the efficient group, with everyone in the inefficient group reporting either "a good deal" or "a great deal" of anxiousness and nervousness. The majority of participants across all study arms found receiving their genetic results helpful and felt they clearly understood

their choices for disease prevention. Additionally, there were low feeling of uncertainty across all study arms in regards to what their genetic results mean to them or their family.

2.4 DISCUSSION

In this intervention study, we returned genetic results on arsenic susceptibility to Bangladeshi research participants with a history of high arsenic exposure, a significant health concern for members of this community. Participants reported that receiving genetic results motivated them to reduce their arsenic exposure. There was an overall reduction in urine arsenic levels relative to their baseline urine arsenic levels among intervention arms, however, there was no statistical difference in this reduction between the intervention arms and the control arm. It is important to note that all 3 study arms received a one-on-one informational intervention that provided participants with information regarding the negative health effects of arsenic exposure and the importance of well-switching to reduce exposure.

All the participants indicated that receiving genetic results was helpful (100%) and overall there was a high participation retention rate (98%), indicating that high-risk individuals from a limited resource setting welcome having access to this information. Similar results have been observed in other low-resource settings, including a study of a minority high-risk population in the United States evaluating genetic risk for 5 complex diseseaes.[90] Prior focus group studies have also found that research participants from underserved backgrounds in the US are interested in receiving genetic results[91, 92]

We found that the efficient arsenic metabolizer (low risk) group, decreased their urine arsenic levels by a similar amount as the control group. This finding is important as there is uncertainty as to how individuals who are told of their low-risk status might behave in terms of

risk aversion. Our study suggests that returning genetic results paired with educational reminders providing information regarding the environmental health risk arsenic was able to limit the participants' feeling of potential invulnerability.

Formal education was low among our participants; however, they appeared to have demonstrated high levels of genetic literacy. These findings suggest that genetic information may be understood by a wide audience if it is tailored appropriately. In our study, the genetic literacy questions were read by the URB staff, and staff were available to answer follow-up questions. Prior studies have proposed that community health workers and patient navigators can be used effectively to disseminate knowledge required to empower disadvantaged communities to benefit from advances in the precision medicine era.[93] In our study, the URB staff, who are native Bangladeshi, knowledgeable about the research and embedded in the community, may have played a similar role in bridging a sense of trust between community members[94] which allowed for increased communication and comprehension regarding their genetic results.

Consistent with our prior survey,[67] nearly all participants feel comfortable sharing genetic results with relatives. This is important as disclosure and communication of participants' genetic results to relatives and even third parties (friends, neighbors, etc.,) may be beneficial given the potential for familial similarity in genetic risk and exposure levels.

When assessing the psychological effects of returning genetic results, participants in the inefficient study arm reported anxiousness and nervousness regarding their genetic results while participants in the control and efficient group did not. However, all participants reported the information to be useful in planning their future. Our results differ from a past study by McCormick et al[95] that found relatively low levels of negative emotional response due to return of genetic results. That study also found that results of modest psychological impact waned over

time.[95] The level of anxiousness felt by the inefficient group may be due in part to the high levels of arsenic present in drinking water in the HEALS community; however, if the psychological impact decreases over time the longer-term utility of the information may outweigh shorter-term emotional responses.

Participants in the inefficient group self-reported higher levels of well-switching in comparison to the other two study arms (p-value <0.001). However, self-reported well switching was not associated with measured changes in urine arsenic levels at six months in any of the study arms. To help provide explanations for this apparent discrepancy, researchers from URB re-contacted 12 participants from the control and the efficient group who had stated they did not switch water sources: 7 of these participants work outside of the community area and tried to drink arsenic free water whenever possible, 3 attempted to preserve rain water, and 2 attempted to collect arsenic free water a few times a week. While this was a small subset of our samples, it suggested that participants in these groups were aware of the harmful effects of arsenic, and some tried to reduce their exposure through methods other than well-switching.

Among participants in the inefficient group who self-reported switching water sources (n=90), ~34% of participants showed no change or an increase in their urine arsenic levels between baseline and the 6-month follow-up. This lack of concordance may be due to social-desirability bias[96] in which some participants in the inefficient group may have over-reported their use of well-switching (the socially desirable behavior). It is also possible that well-switching did not produce exposure reductions in cases where a participant's new well did not have an arsenic concentration substantially lower than the participant's previous well.

In this study, we recruited a subset of HEALS participants with recent evidence of high arsenic exposure. In other words, participants included in this study do not appear to have

benefited from past community-level educational interventions in HEALS, which were effective for reducing arsenic exposure in the past.[97, 98] In this study, all participants received a one-on-one health promotion informational intervention. Given the clear arsenic exposure reduction observed in the control group the one-on-one intervention may have higher efficacy then prior community-level interventions in HEALS. The strong efficacy of this intervention likely contributes to the lack of effect of observed for the return of genetic results intervention over and above the informational intervention.

This study is novel in that it has implemented an intervention to return genetic results in a low-resource population setting with low educational backgrounds and a specific environmental exposure within their community. Returning genetic results to diverse socio-demographically diverse populations is important to the scientific community's commitment to increase the diversity of research participants in genomic studies. In addition, the genetic results we provide are relevant to a specific environmental exposure. This is unique in the return of results literature, and the genetic information we return is of unique concern to this community with long-term exposure to arsenic.

A limitation of our study is that our results are based on a single follow-up measure of arsenic at 6 months which is a snapshot of the potential behavioral changes that have occurred and therefore may not be representative of the long-term effects of the intervention. A study by Arkadianos et al., found that when providing genetic information as an intervention for behavioral change participants in the intervention arms produced positive behavior changes after observing the behavioral change for a longer period of time (>300 days) compared to the control group who did not receive genetic information.[99, 100] Therefore, while our study has currently observed a similar decrease in urine arsenic levels by all study arms, this decrease could differ

across groups over time. Additional studies are needed to examine the impact of return of genetic results across longer periods of time in under resourced and high-risk populations on health behaviors.

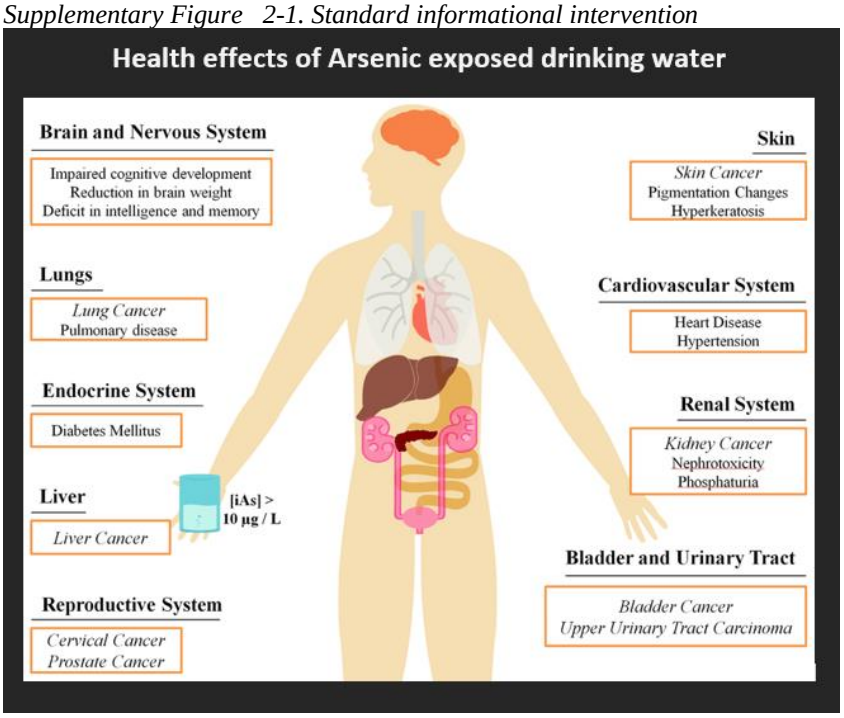
An additional limitation of this study is our lack of data on specific wells people switched to (and the new well's arsenic concentration). Arsenic in drinking water has been shown to have a strong correlation with urine arsenic levels ($r=0.5$)[101] , therefore, well arsenic concentration would provide us insights to view potential discrepancies between well-switching and urine arsenic exposure reduction. While tracking changes in drinking wells had been a part of the initial study design, it was not feasible to obtain well IDs due to participants either not having the information or the wells not being well labeled. We also did not collect data on other methods of exposure reduction, such as rain harvesting. Given the observed inconsistencies between self-reported well-switching and measured urine arsenic levels, there may have been other exposure reduction strategies contributing to the observed decreases in arsenic exposure.

In the context of returning genetic results, there exist regulations and guidelines that govern this process[102, 103]. These regulations aim to ensure responsible and ethical practices in handling and disclosing genetic information. However, it is important to note that low- and middle-income country (LMIC) settings may not have the same level of regulatory infrastructure as higher income countries[104]. Despite this, it is crucial to make efforts to adhere to the available guidelines when returning genetic results in LMICs. While challenges may exist due to limited resources, infrastructure, and expertise in genetic counseling, it is essential to work towards overcoming these barriers in order to uphold the principles of responsible genetic result disclosure in LMIC settings. Collaboration and adaptation of guidelines to fit the specific context of LMICs can help navigate these challenges and ensure the responsible return of genetic results.

2.5 CONCLUSION

This study examined the effects of returning genetic results related to susceptibility to arsenic exposure to Bangladeshi research participants. Similar to prior studies, we show that participants in a low-resource setting are interested in genetic results and find them useful. However, our study did not show that returning genetic results increased the impact of a one-on-one educational intervention for reducing arsenic exposure. Moreover, we found that disclosing a "low-risk" genetic status did not reduce participants' willingness to decrease their arsenic exposure when coupled with an appropriate educational intervention. Finally, returning genetic results increased self-reported exposure-reducing behaviors but did not have a detectable impact on reducing urine arsenic over and above a one-on-one educational intervention.

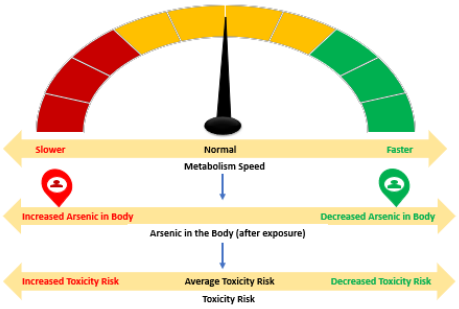
Supplementary Figure 2-1. Standard informational intervention

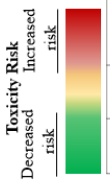


Supplementary Figure 1. Standard informational intervention

Supplementary Figure 2-2. Return of Genetic Results Fact Sheet

- Arsenic consumed is gradually removed from the body in urine
- Arsenic "metabolism" is a process that helps remove arsenic from the body
- People remove arsenic from their bodies at different speeds due to inherited differences in genes that affect arsenic metabolism





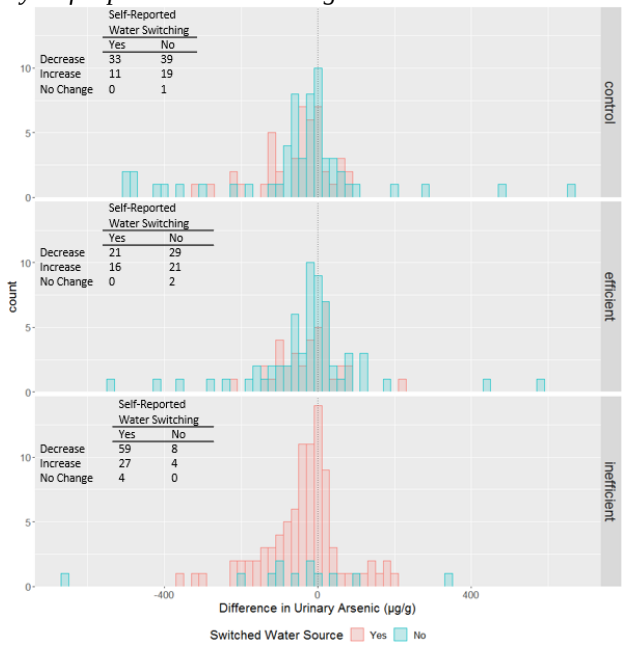
Metabolizer Group	
Inefficient Metabolizers	Arsenic removed from body more slowly compared to others. This could lead to increased risk for arsenic toxicities.
Normal Metabolizers	Arsenic is removed from your body at an average rate
Efficient Metabolizers	Arsenic is removed from your body faster than most other people. This could lead to decreased toxicity risk.

Message for Inefficient metabolizer:
Based on your genes, you are a slow metabolizer of arsenic. Keeping your arsenic exposure low is important for your health, likely more important for you than most others in your community.

Message for Efficient/Average metabolizer:
Based on your genes, you are NOT a slow metabolizer of arsenic
Keeping your arsenic exposure low is still important for your health, however, your risk for arsenic toxicities is similar to most others in the community

Supplementary Figure 2. Return of Genetic Results Fact Sheet

Supplementary Figure 2-3. Change in urine arsenic levels by self-reported well switching



Supplementary Figure 3. Change in urine arsenic levels by self-reported well switching.

Supplementary Table 2-1. Pre-intervention survey question responses regarding attitudes towards return of genetic results

Supplementary Table 1. Pre-intervention survey question responses regarding attitudes towards return of genetic results (n=309, HEALS)					
	Overall	Control	Efficient	Inefficient	P
Variable*	309	103	103	103	
Q1. Concerned about arsenic-contaminated drinking water? (%)					
Yes	300 (97.1)	98 (95.1)	101 (98.1)	101 (98.1)	0.36
No	9 (2.9)	5 (4.9)	2 (1.9)	2 (1.9)	
Q2. Interested in knowing if your genes make you susceptible to arsenic toxicity? (%)					
Yes	307 (99.4)	102 (99.0)	102 (99.0)	103 (100.0)	0.61
No	2 (0.6)	1 (1.0)	1 (1.0)	0 (0.0)	
Q3. Is your primary water source believed to be "arsenic free"? (%)					
Yes	41 (13.3)	19 (18.4)	13 (12.6)	9 (8.7)	0.01
No	149 (48.2)	52 (50.5)	39 (37.9)	58 (56.3)	
Don’t Know	119 (38.5)	32 (31.1)	51 (49.5)	36 (35.0)	
Q4. Can you take action to reduce arsenic in drinking and cooking water for you/your family? (%)					
Yes	277 (89.6)	87 (84.5)	93 (90.3)	97 (94.2)	0.07
No	32 (10.4)	16 (15.5)	10 (9.7)	6 (5.8)	
Q5. Would gene-based arsenic risk information motivate you to use less arsenic-contaminated water for your family? (%)					

Yes	304 (98.4)	100 (97.1)	101 (98.1)	103 (100.0)	0.24
No	5 (1.6)	3 (2.9)	2 (1.9)	0 (0.0)	
Q6. Comfortable sharing gene-based arsenic risk with family if elevated? (%)					
Yes	306 (99.0)	101 (98.1)	102 (99.0)	103 (100.0)	0.36
No	3 (1.0)	2 (1.9)	1 (1.0)	0 (0.0)	
Q7. Would you keep gene-based arsenic risk confidential from non-family members if elevated? (%)					
Yes	71 (23.0)	27 (26.2)	22 (21.4)	22 (21.4)	0.63
No	238 (77.0)	76 (73.8)	81 (78.6)	81 (78.6)	
Values are n (%) *Survey questions shorted for manuscript					

Supplementary Table 2-2. Genetic Comprehension Survey

Supplementary Table 2. Genetic Comprehension Survey					
	Overall	control	efficient	inefficient	P-value
n	309	103	103	103	
If your close relative has a disease (such as diabetes or heart disease), you are more likely to develop the disease (TRUE) (%)					
Incorrect	16 (5.2)	6 (5.8)	6 (5.8)	4 (3.9)	0.768
Correct	293 (94.8)	97 (94.2)	97 (94.2)	99 (96.1)	
What you inherit from your parents impacts your health (TRUE) (%)					
Incorrect	26 (8.4)	5 (4.9)	12 (11.7)	9 (8.7)	0.211
Correct	283 (91.6)	98 (95.1)	91 (88.3)	94 (91.3)	
A healthy lifestyle can prevent or lessen the negative consequences of having genetic predispositions to some diseases (TRUE) (%)					
Incorrect	3 (1.0)	2 (1.9)	0 (0.0)	1 (1.0)	0.364
Correct	306 (99.0)	101 (98.1)	103 (100.0)	102 (99.0)	
The environment has little or no effect on how genes contribute to disease (FALSE) (%)					
Incorrect	264 (85.4)	92 (89.3)	82 (79.6)	90 (87.4)	0.112
Correct	45 (14.6)	11 (10.7)	21 (20.4)	13 (12.6)	
Can drinking arsenic-contaminated drinking water lead to health effects? (TRUE) (%)					
Incorrect	3 (1.0)	0 (0.0)	2 (1.9)	1 (1.0)	0.364
Correct	306 (99.0)	103 (100.0)	101 (98.1)	102 (99.0)	
Can genes provide you information on your susceptibility to arsenic toxicities? (TRUE) (%)					
Incorrect	25 (8.1)	8 (7.8)	9 (8.7)	8 (7.8)	0.957
Correct	284 (91.9)	95 (92.2)	94 (91.3)	95 (92.2)	
Score (%)					
3	10 (3.2)	4 (3.9)	4 (3.9)	2 (1.9)	0.394
4	27 (8.7)	4 (3.9)	13 (12.6)	10 (9.7)	
5	34 (11.0)	12 (11.7)	12 (11.7)	10 (9.7)	
6	238 (77.0)	83 (80.6)	74 (71.8)	81 (78.6)	
Values are n (%)					

Supplementary Table 2-3. Participants in same households by study arm

Supplementary Table 3. Participants in same households by study arm			
	# Spouse Pairs	Ave. UrAsCr Baseline (µg/g)	Ave. UrAsCr 6-month-Follow-up (µg/g)
Control-Control	4	59.27	73.63
Efficient-Efficient	6	72.23	44.56
Inefficient-Inefficient	2	25.03	36.44
Control-Efficient	5	324.29 (control)	59.76 (control)
		154.92 (efficient)	86.9 (efficient)
Control-Inefficient	6	83.44 (control)	29.05(control)
		152.57(inefficient)	75.97 (inefficient)
Efficient-Inefficient	6	142.45 (efficient)	75.27 (efficient)
		14.69 (inefficient)	73.25 (inefficient)
*UrAsCr: Urinary arsenic adjusted for creatinine			

Supplementary Table 2-4. Participant FACToR Questionnaire responses*

Supplementary Table 4. Participant FACToR* Questionnaire responses			
	Efficient	Inefficient	p-value
	101	102	
How anxious or nervous did you feel about your genetic test result? (%)			
Not at all	98 (97.0)	0 (0.0)	<0.001
A little	2 (2.0)	0 (0.0)	
Somewhat	1 (1.0)	0 (0.0)	
A good deal	0 (0.0)	23 (22.5)	
A great deal	0 (0.0)	79 (77.5)	
How much did you feel that you understood clearly your choices for disease prevention? (%)			
A good deal	13 (12.9)	7 (6.9)	0.230
A great deal	88 (87.1)	95 (93.1)	
How helpful was the information you received from your genetic test result in planning for the future? (%)			
A good deal	47 (46.5)	31 (30.4)	
A great deal	54 (53.5)	71 (69.6)	0.026
How uncertain did you feel about what your genetic test result means for you? (%)			
Not at all	92 (91.1)	98 (96.1)	0.244
A little	9 (8.9)	4 (3.9)	
How uncertain did you feel about what your genetic test result means for your family?(%)			
Not at all	67 (66.3)	81 (79.4)	0.023
A little	34 (33.7)	19 (18.6)	
Somewhat	0 (0.0)	2 (2.0)	
* FACToR: Feelings About genomiC Testing Results			

Chapter 3 ASSESMENT OF CANCER SCREENING BEHAVIORS AND BREAST CANCER FAMILY HISTORY IN SPANISH-SPEAKING HISPANIC/LATINA WOMEN IN CALIFORNIA: INSIGHTS FOR GENETIC SCREENING AND PREVENTION

Tamayo LI, Perez F, Perez A, Hernandez M, Martinez A, Huang X, Zavala VA, Ziv E, Neuhausen SL, Carvajal-Carmona LG, Duron Y. Cancer screening and breast cancer family history in Spanish-speaking Hispanic/Latina women in California. Frontiers in oncology. 2022 Oct 26;12:940162.

3.1 INTRODUCTION

Breast cancer is the most common cancer among women in the United States[105, 106] and the leading cause of cancer death among Hispanics/Latinas (H/L)[107]. Furthermore, H/L are less likely than Non-H/L White (NHW) women to be diagnosed in the early stages of disease and are less likely to have access to high-quality care because of factors such as lower socioeconomic status (SES), high uninsured rate,[107, 108] and issues communicating with providers.[109] Additionally, among women of all ages dying of breast cancer, H/L have a 164% higher risk of dying before the age of 50 years in comparison with NHW women.[110]

Approximately 5-10% of breast cancer cases can be attributed to inherited genetic mutations[111]. Women with pathogenic variants in high penetrance genes such as *BRCA1* and *BRCA2* have a 40-80% lifetime risk of breast cancer compared to 12% risk in the general population.[112] Only about 10% of mutation carriers are aware of their mutation status.[113] While awareness[114] and use[115] of genetic testing in different populations has increased over time, disparities in access to hereditary breast cancer risk assessment, genetic counseling, and genetic testing continue to exist in the United States (U.S.),[116] with awareness among H/L being particularly low (33.2%) compared to NHW women (51.9%, $p<0.0001$) based on data from the 2010 National Health

Interview Survey.[113, 114, 117] Screening for pathogenic mutations can open opportunities for cancer prevention and/or engagement in frequent cancer screening to detect it early.[118] Past studies have shown that genetic counseling can help women and their families make informed decisions about genetic testing and early cancer detection or risk-reduction strategies.[119, 120] Genetic counseling and testing for breast cancer survivors also is critically important as it can inform targeted treatment, risk management for second primary cancers, and targeted cascade testing for at-risk family members.[121] An analysis including 64,717 women who underwent genetic screening between the years 2006-2007 demonstrated that the mutation rate of BRCA1 and BRCA2 was about the same in H/L and NHW women;[122, 123] however, H/L were 3.9-4.8 times less likely to undergo genetic testing than NHW women.[123] The lower use of genetic testing in H/L and other underrepresented populations compared to NHW women reduces the generalizability of genetic discoveries and leads to challenges in interpreting genetic results.[124]

Lack of insurance and economic concerns often are the main barriers for obtaining a genetic risk assessment for hereditary breast and ovarian cancer, and limited English proficiency and cultural factors such as embarrassment, modesty and secrecy also reduce the rate of genetic testing.[125] H/L are willing to engage and have a strong desire for counseling and screening despite barriers they experience,[125-129] however, within a study of 1622 participants recruited through a state cancer registry and who reported receiving genetic testing, H/L were nearly two times less likely as NHW women to report discussing genetic testing with a health provider.[130, 131] A study on H/L found positive attitudes towards genetic testing for cancer prevention, with 87% agreeing it was a good idea and 87.7% agreeing that everyone should get genetic testing for cancer prevention.[132] Another study focused on low income women in California, including H/Ls, identified participants at high-risk for hereditary breast and ovarian cancer via a phone

intervention and reported that 39% accepted and received genetic counseling during the intervention period.[133]

Community health educators (*promotores*) are uniquely positioned to bridge the gap between the H/L community and the health care system.[134-138] Promotores are typically from the community in which they work, speak the same language, and understand the culture's idiosincracies.[136] They are able to translate medical jargon into practical, realistic steps that can be better understood and followed by members of their communities.[138] Promotores-led educational interventions are cost-effective in increasing cancer screenings in the H/L community.[139-143] Interventions led by promotores significantly increase breast cancer-related knowledge among participants.[141, 144]

There is currently limited work on increasing breast and ovarian cancer genetic screening among H/L.[114, 117, 128, 145-147] To address this gap, the research team in partnership with The Latino Cancer Institute developed a program, "Tu Historia Cuenta" (THC), to conduct outreach and educate the H/L community, particularly targeting monolingual Spanish-speaking women.[148] Materials were developed to train promotores about hereditary breast cancer as well as to facilitate the interaction between promotores and the community. In this paper, we provide a description of the demographic characteristics of the participants in the program and the results of the breast cancer family history and feedback surveys which highlights the need for further improvement in hereditary breast and ovarian cancer screening in this population.

3.2 METHODS

3.2.1 Study population

Recruitment of participants started in June 2020 and was led by two promotores organizations in Southern and Northern California.[149, 150] As of March 2022, 1062 H/L in California had registered for the THC education session. Of these, 1042 answered the demographic survey, 891 participants answered the breast cancer family history survey, and 525 participants answered the feedback survey. The demographic survey was provided to women after registration, before the educational session. Participants were asked to answer the cancer family history survey after the education session as to maximize their comprehension of the reason for those questions and how to respond to them. As a result, a small number of participants (N=20) registered for the education session but did not complete the demographic survey and 14% (N=151) of participants attended the education session but did not answer the family history survey.

The current report is based on all survey responses available on March 18th, 2022. The inclusion criteria for participants were 1) women 21-75 years of age, 2) Spanish-speaking or bilingual, and 3) self-identifying as H/L. Participants provided verbal informed consent. Data from all surveys were de-identified. The study was approved by the University of California, San Francisco Institutional Review Board.

3.2.2 Program description

THC is a promotores-led outreach and education program with materials developed using a continuous stakeholder engagement approach as previously described.[148] The one-hour educational sessions provide participants basic background knowledge on breast cancer with a particular focus on hereditary breast cancer and genetics.[148] THC participants completed three surveys: 1) a demographic information and general cancer screening history (i.e., mammography screening, colorectal cancer screening, cervical cancer screening) and exposure to genetic testing

(i.e., cancer risk assessment) survey, 2) a breast/ovarian cancer-specific family history survey aimed at identifying women at higher risk of hereditary breast/ovarian cancer[151] that was adapted from the Pedigree Assessment Tool[152, 153], and 3) the post-education session feedback survey which assessed the utility, quality, and compressibility of the educational session components. The family history survey was selected for its ease of administration and its previous validation in low income population including H/L which was done by comparing it to genetic counselors' assessments[154] and to Referral screening tools (RST).[152] When researchers compared the family history survey to RST, the survey had high sensitivity (~92%), specificity (0.94%) and high AUROC (98%); additional details can be found elsewhere.[155] Each 'Yes' response on the survey had an associated score of 2, 4, or 6 depending on the age of onset and type of cancer reported for self and family member. Participants with a scores of 6 or higher were considered to have responded in a manner consistent with a strong family history of breast/ovarian cancer.

Women identified as having strong family history based on their score in the breast cancer-family history survey received a recommendation to discuss their family history with a doctor and potentially a genetic counselor. For those without a usual source of care, we provided resources and support to facilitate access.

3.2.3 Survey Content

The demographic survey contained questions including city of residence, zip code, age, number of years residing in the U.S., number of people in the household, and employment status. Information regarding English-language proficiency (a. monolingual Spanish speaker, b. limited English use, c. conversational English, d. fully bilingual), medical insurance (a. no insurance, b. public insurance, c. private insurance), and educational attainment (a. no school, b. elementary school, c. middle school, d. high school, e. associate degree, f. university degree) was obtained.

In addition, the demographic survey contained questions regarding genetic testing such as previous knowledge and exposure to genetic testing, and interest in genetic testing. A subset of questions targeted cancer screening behavior (i.e., breast, cervical, and colorectal cancer screening).

The family history of breast cancer survey was adapted from a previously validated survey[155] and collected the following information on the participant and their first- and second-degree relatives: breast cancer diagnoses before age 50 years, after age 50 years, and cancer in both breasts. This survey included additional questions on family history of ovarian cancer, three or more family members on the same side of the family with cancer of the breast, prostate, and/or pancreas, and male family member with breast cancer. At the end of the survey, participants were asked about their willingness to be contacted in the future to learn more about their respective cancer risk if they were identified as having a strong family history of breast cancer.

The feedback survey was given to participants at the end of the education session. This survey was anonymous and had nine questions to help understand how useful participants found the information provided and whether they felt motivated to share the information learned with family and friends and to seek additional information regarding breast cancer.

3.2.4 Data Analysis

Average, dispersion (standard deviation-SD) and proportion measures were used to describe the characteristics of the participants and their survey responses. We used chi-square, Fisher's exact test, and two-sided t-tests to compare characteristics and responses between

participants in the three areas of outreach: San Francisco, Sacramento, and Los Angeles County, as well as by breast cancer family history score (a. <6, b.6+) and screening status.

We used multivariate multinomial logistic regression analyses to assess the association between different demographic factors and screening behavior among THC participants. The 'never' screened category group was defined as reference in all regression models. All analyses were conducted in RStudio version 4.1.2.[156]

3.3 RESULTS

3.3.1 Participants' demographic characteristics

A total of 1042 Spanish-speaking H/L women residing in San Francisco County, Sacramento and Los Angeles provided demographic information after registering for the THC education session. The average age of participants was 43 years and ranged between 21 and 73 years (Table 1). Most individuals were born outside the United States (86.1%) and had lived in the US for an average of 18 years (Min: 1 year, Max: 54 years). Approximately 6.5% of participants reported no formal education, 22.6% graduated from elementary school only, 16.3% middle school, 32.1% high school, 11.9% had an associate degree and 9.1% a university degree. The program's target population was Spanish-speaking H/L, which was reflected by the responses related to English language proficiency: 17.7% were monolingual Spanish-speakers, 30.7% had basic knowledge of English, 36.9% conversational English, and 14.2% were fully bilingual. Half of the participants (50.0%) had public health insurance, 35.8% had no insurance, and 13.4% had private insurance. The average number of individuals leaving in the participants' household was 4.3 (SD= 2.1).

3.3.2 Differences in demographic characteristics between participants in Los Angeles, Sacramento, and San Francisco

Average age of participants varied between the Los Angeles County, Sacramento, and San Francisco recruitment groups, with San Francisco individuals having the lowest mean age (44.7, 42.3, and 40.5 years respectively) (Table 1). Participants from San Francisco had been in the US for an average of 16 years (SD=12), which was lower than the number of years reported by participants in Los Angeles County and Sacramento (20 years, SD=10, and 19 years, SD=8, respectively). Furthermore, San Francisco had the largest proportion of participants with at least conversational English language proficiency and high school education or higher (Table 1). In Los Angeles County and Sacramento, participants were more likely to report being uninsured (44.0%, 44.3%) compared to San Francisco (9.3%). San Francisco participants were more likely to report having public health insurance (77.0% vs. 36.0% for Sacramento and 44.3% for Los Angeles County) (Table 1). On average, participants in Sacramento lived in larger households (4.6 people) compared to participants in Los Angeles County (4.4 people) and San Francisco (3.8 people) (Table 1).

Table 3-1. Demographic characteristics of 1042 'Tu Historia Cuenta' program participants in California overall and by recruitment area.

Variable, N (%) or Mean (SD)	Overall	Los Angeles	Sacramento	San Francisco	p-value
Number of participants	1042 (100)	530 (50.9)	264 (25.3)	248 (23.8)	
Age in years	43.06 (10.24)	44.68 (10.22)	42.26 (9.14)	40.47 (10.79)	<0.001
Place of birth					
Foreign-born	897 (86.1)	420 (79.2)	250 (94.7)	227 (91.5)	<0.001
US-born	101 (9.7)	73 (13.8)	13 (4.9)	15 (6.0)	
Missing	44 (4.2)	37 (7.0)	1 (0.4)	6 (2.4)	
Years in the United States	18.87 (10.15)	20.43 (9.94)	19.27 (8.25)	15.56 (11.63)	<0.001
English Language Proficiency					
Monolingual Spanish Speaker	184 (17.7)	111 (20.9)	35 (13.3)	38 (15.3)	0.015
Limited English Use	320 (30.7)	152 (28.7)	97 (36.7)	71 (28.6)	
Conversational	384 (36.9)	185 (34.9)	91 (34.5)	108 (43.5)	
Fully Bilingual	148 (14.2)	76 (14.3)	41 (15.5)	31 (12.5)	
Missing	6 (0.6)	6 (1.1)	0 (0.0)	0 (0.0)	
Health Insurance Status					
No Insurance	373 (35.8)	233 (44.0)	117 (44.3)	23 (9.3)	<0.001
Public	521 (50.0)	235 (44.3)	95 (36.0)	191 (77.0)	
Private	140 (13.4)	54 (10.2)	52 (19.7)	34 (13.7)	
Missing	8 (0.8)	8 (1.5)	0 (0.0)	0 (0.0)	
Educational Attainment					
No school	68 (6.5)	55 (10.4)	3 (1.1)	10 (4.0)	<0.001
Elementary School	235 (22.6)	134 (25.3)	75 (28.4)	26 (10.5)	
Middle School	170 (16.3)	50 (9.4)	78 (29.5)	42 (16.9)	
High School	335 (32.1)	169 (31.9)	60 (22.7)	106 (42.7)	
Associate Degree	124 (11.9)	55 (10.4)	26 (9.8)	43 (17.3)	
University	95 (9.1)	54 (10.2)	22 (8.3)	19 (7.7)	
Missing	15 (1.4)	13 (2.5)	0 (0.0)	2 (0.8)	
Number of People in Household	4.32 (2.09)	4.41 (2.33)	4.62 (1.53)	3.84 (1.98)	<0.001

3.3.3 Screening Behavior and Knowledge about Genetic Testing

Most participants expressed interest in learning about genetics (98%), and only 1.3% of the individuals stated that they were not interested in learning about genetics or how genetics

could be used to prevent or detect cancer early. More than half of the participants reported that they had not heard about genetic tests before (52.2%) (Table 2).

Among women within the age range of mammography screening guidelines (40-74 years), 56.1% were current with their mammogram (i.e., mammogram within the last 2 years), and 42.8% of the participants were due for mammograms (i.e., never had obtained a mammogram or their last mammogram was done more than 2 years ago). Of the 163 women who had never had a mammogram, 14% were navigated into the Every Women Counts program (EWC),[157] and of the 109 women who had their mammogram more than 2 years ago, 38% were navigated into this program. It is important to note that the THC education session included information about the EWC program that was shared with all participants. Due to this, women who had not previously received mammograms may not have expressed a need for navigation assistance but still taken advantage of the EWC program.

Cervical cancer screening for women between the ages of 21 to 65 years was observed for 82.1%, with 73.3% of the participants having obtained a Papanicolaou test within the last 3 years. Among participants 50 years of age and older, 23.5% reported ever having colorectal cancer screening (Table 2).

3.3.4 Differences in screening behavior and genetic testing knowledge between participants in Los Angeles County, Sacramento, and San Francisco

Most participants in the program expressed interest in learning about genetics and breast cancer (~98%), however, a larger proportion of participants who resided in the San Francisco area were aware of genetic testing (62.9%) compared to participants in Los Angeles County (42.3%) and Sacramento (41.3%) (Table 2).

A similar proportion of participants in Sacramento and San Francisco were up to date with mammography screening (60.6% and 60.8%, respectively), while a lower proportion was observed among participants in Los Angeles County (52.5%); this difference was not statistically significant (Table 2).

Differences between regions in cervical and colorectal cancer screenings were not statistically significant (Table 2). However, San Francisco had the highest proportion of participants reporting a Papanicolaou test within the last 3 years (84.9%), followed by Sacramento (79.3%) and Los Angeles County (64.8%). Similarly, 30% of participants from San Francisco who were 50 years and older obtained colorectal cancer screenings, followed by 25% of participants in Sacramento and 20.9% in Los Angeles County (Table 2).

Table 3-2. Screening behavior and interest in breast cancer genetics among 'Tu Historia Cuenta' study participants (N=1042) overall and by recruitment area.

Interest and awareness, N (%)	Overall	Los Angeles	Sacramento	San Francisco	P-value
Number of Participants	1042 (100)	530 (50.9)	264 (25.3)	248 (23.8)	
Interest in learning about genetics and BC					
No Interest	14 (1.3)	11 (2.1)	0 (0.0)	3 (1.2)	<0.001
Some Interest	220 (21.1)	149 (28.1)	23 (8.7)	48 (19.4)	
Very Interested	801 (76.9)	364 (68.7)	240 (90.9)	197(79.4)	
Missing	7 (0.7)	6 (1.1)	1 (0.4)	0 (0.0)	
Genetic Testing Awareness					
Yes	489 (46.9)	224 (42.3)	109 (41.3)	156 (62.9)	<0.001
No	544 (52.2)	297 (56.0)	155 (58.7)	92(37.1)	
Missing	9 (0.9)	9 (1.7)	0 (0.0)	0 (0.0)	
Cancer Screening					
Breast Cancer Screening (Age 40 to 74)	636	356	160	120	
Up to date with mammogram (<2 years ago)	357 (56.1)	187 (52.5)	97 (60.6)	73 (60.8)	0.200
Due for mammogram (never or 2+ years ago)	272 (42.8)	162 (45.5)	63 (39.4)	47 (39.2)	
Missing	7 (1.1)	7 (2.0)	0 (0.0)	0 (0.0)	
Connected to EWC Program (of those due for mammogram)	64 (23.5)	53 (32.7)	10 (15.9)	1 (2.1)	<0.001
Cervical Cancer Screening (Age 21 to 65)	1012	512	261	239	
Ever had a pap smear	831 (82.1)	380 (74.2)	233 (89.3)	218(91.2)	<0.001
Up to date with pap smear	742 (73.3)	332 (64.8)	207 (79.3)	203 (84.9)	0.103
Due for Pap. Test (never or 3+ years ago)	250 (24.7)	165 (16.3)	52 (5.1)	15 (1.4)	
Missing	19 (1.9)	14 (2.7)	2 (0.8)	3 (1.3)	
Colorectal Cancer Screening (Age 50+)	264	158	56	50	
Up to date with colonoscopy	62 (23.5)	33 (20.9)	14 (25.0)	15 (30.0)	0.355
Due for colonoscopy	189 (71.6)	116 (73.4)	42 (75.0)	31 (62.0)	
Missing	13 (4.9)	9 (5.7)	0 (0.0)	4 (8.0)	

3.3.5 Demographic Characteristics and Cancer Screening Behavior

Participant's age, years residing in the United States, English language proficiency level, health insurance status, educational attainment, and number of residents in the household were all associated with screening behavior (Table 3). In general, screening was more common among bilingual participants with health insurance and formal education. Educational attainment was strongly associated with colorectal cancer screening, with up to 52% of individuals with a university degree reporting colorectal cancer screening compared to 21% of those with only elementary education and 0% of those with no formal education (Table 3). Education was also associated with cervical cancer screening; the largest proportion of women reporting never having had a Papanicolaou test were those with no formal education (29%) (Table 3). English proficiency and insurance status were associated with breast cancer screening; the lowest proportion of current mammograms was reported by monolingual Spanish speakers (42%) and the highest among those with private health insurance (72%) (Table 3).

Variable	Mammography Screening* Mean (SD) or N (%)				Cervical Cancer Screening* Mean (SD) or N (%)				Colorectal Cancer Screening* Mean (SD) or N (%)		
	Up to Date	>2 years	Never	P-value	Up to Date	>3 years	Never	P-value	Yes	No	P-value
	357 (56)	109 (17)	163 (26)		742 (73)	88 (8)	162 (16)		62 (24)	189 (72)	
Age, years	50.5 (7.3)	51.3 (7.7)	45.5 (6.7)	<0.001	42.2 (9.2)	43.7 (8.2)	42.2 (10.8)	0.360	57 (6)	56 (6)	0.312
Year in United States	23.2 (9.6)	21.0 (9.7)	19.0 (8.5)	<0.001	18.2 (8.9)	20.7 (10.0)	18.4 (11.0)	0.113	28 (10)	24 (10)	0.010
Place of birth											
Foreign-born*	316 (57)	95 (17)	139 (25)	0.91	652 (76%)	71 (8)	131 (15)	0.077	54 (24%)	169 (76)	0.43
US-born	28 (56)	8 (16)	14 (28)		65 (66%)	10 (10)	23 (23)		7 (35%)	13 (65)	
missing	13 (45)	6 (21)	10 (34)		25 (62%)	7 (18)	8 (20)		1 (12%)	7 (88)	
English Language Proficiency											
Monolingual Spanish Speaker	45 (42)	22 (21)	39 (37)	0.015	114 (68)	16 (10)	38 (23)	0.003	7 (15)	41 (85)	0.01
Limited English Use	130 (59)	43 (20)	46 (21)		235 (75)	36 (12)	41 (13)		22 (24)	68 (76)	
Conversational	132 (58)	35 (15)	59 (26)		294 (80)	22 (6)	51 (14)		18 (22)	63 (78)	
Fully Bilingual	49 (64)	8 (11)	19 (25)		97 (68)	14 (10)	32 (22)		15 (47)	17 (53)	
Missing data	1 (50)	1 (50)	0 (0)		2 (100)	0 (0)	0 (0)		0 (0.0)	0 (0.0)	
Health Insurance											
No Insurance	104 (47)	45 (20)	73 (33)	<0.001	240 (67)	49 (14)	68 (19)	<0.001	11 (14)	67 (86)	0.013
Public	183 (60)	47 (15)	76 (25)		381 (77)	31 (6)	84 (17)		34 (27)	92 (73)	
Private	69 (72)	14 (15)	13 (14)		117 (87)	8 (6)	10 (7)		17 (37)	29 (63)	
Missing data	1 (20)	3 (60)	1 (20)		4 (100)	0 (0)	0 (0)		0 (0)	1 (100)	
Educational Attainment											
No school	22 (44)	11 (22)	17 (34)	0.410	36 (64)	4 (7)	16 (29)	0.030	0 (0)	36 (100)	<0.001
Elementary School	84 (58)	19 (13)	42 (29)		167 (74)	16 (7)	43 (19)		12 (21)	45 (79)	
Middle School	51 (51)	23 (23)	26 (26)		128 (76)	19 (11)	21 (12)		4 (12)	30 (88)	
High School	117 (60)	31 (16)	47 (24)		255 (79)	27 (8)	40 (12)		19 (30)	44 (70)	
Associate Degree	45 (60)	13 (17)	17 (23)		81 (69)	16 (14)	21 (18)		12 (38)	20 (62)	
University	38 (63)	10 (17)	12 (20)		68 (73)	6 (6)	19 (20)		15 (52)	14 (48)	
Missing data	0 (0)	2 (50)	2 (50)		7 (78)	0 (0)	2 (22)		0 (0)	0 (0)	
Number of People in Household	4.08 (1.8)	3.91 (1.8)	4.6 (1.7)	0.003	4.3 (1.9)	4.4 (1.9)	4.2 (1.9)	0.703	3 (2)	4 (2)	<0.001

*The sample sizes for each screening rate is based on women who answered the survey between targeted age groups: Mammography screening 40-74 years, Cervical cancer screening 21-65 years and Colorectal cancer screening ages 50+

Multiple factors were associated with mammography screening behavior in multivariate analysis. Age, educational attainment, English fluency and having private insurance were positively associated with being up-to-date with screening (Table 4). Additionally, program participants from Sacramento were approximately 2-fold more likely to be current with mammography screening in adjusted models compared to those from Los Angeles County (P-value 0.008).

Table 3-4.Multivariate multinomial logistic regression model testing the association between breast cancer screening behavior and demographic factors among 'Tu Historia Cuenta' participants ages 40 to 74. (N=587, 41 excluded from 629 due to missing data)

Variable	RRR*	L95%CI	H95%CI	P-value
Never had mammography (reference)				
Mammography up to date				
Age	1.17	1.12	1.22	<0.001
Years residing in the US	0.98	0.95	1.01	0.175
Immigration status (US born vs. foreign born)	0.95	0.34	2.61	0.917
Educational Attainment (ref: no schooling)				
Elementary	2.56	1.00	6.53	0.050
Middle school	1.54	0.52	4.53	0.435
High school	3.00	1.10	8.20	0.032
Associate degree	2.07	0.66	6.48	0.211
University degree	2.28	0.68	7.62	0.182
Region of residence (ref: Los Angeles)				
Sacramento	2.16	1.23	3.81	0.008
San Francisco	1.08	0.58	2.03	0.801
Insurance Status (ref: no insurance)				
Public	1.58	0.98	2.57	0.062
Private	3.19	1.46	6.98	0.004
English Fluency (ref: monolingual)				
Limited English Use	2.38	1.14	4.99	0.021
Conversational	2.16	1.10	4.25	0.026
Fully Bilingual	1.84	0.69	4.91	0.225
Number of people in the household	0.90	0.78	1.02	0.102
Mammography more than 2 years ago				
Age	1.18	1.12	1.25	<0.001
Years in the US	0.97	0.94	1.01	0.118
Immigration status	0.94	0.23	3.79	0.927
Educational Attainment (ref: no schooling)				
Elementary	1.41	0.45	4.48	0.555
Middle school	2.05	0.55	7.63	0.283
High school	2.38	0.69	8.25	0.171
Associate degree	2.43	0.60	9.84	0.214
University degree	2.13	0.48	9.49	0.319
Region of residence (ref: Los Angeles)				
Sacramento	2.33	1.14	4.75	0.020
San Francisco	0.84	0.36	1.94	0.678
Insurance Status (ref: no insurance)				
Public	0.99	0.54	1.84	0.987
Private	1.63	0.61	4.33	0.329
English Fluency (ref: monolingual Spanish)				
Limited English Use	1.60	0.65	3.98	0.307
Conversational	1.18	0.51	2.76	0.694
Fully Bilingual	0.42	0.10	1.71	0.226
Number of people in the household	0.84	0.70	0.99	0.039

*Relative Risk Ratio.

Cervical cancer screening behavior was statistically significantly different when comparing participants in Los Angeles County to those in the Northern California cities, with the latter having a higher relative risk of being up to date (P-value <0.001) (Table 5). Participants with private insurance were 3.7 times more likely to be up to date with cervical cancer screening compared to those without health insurance (P-value 0.001).

Table 3-5. Multivariate multinomial logistic regression model testing the association between cervical cancer screening behavior and demographic factors among 'Tu Historia Cuenta' participants ages 21 to 65 (N=932, 80 excluded from 1012 due to missing data)

Variable	RRR*	L95%	H95%	P-Value
Never had cervical cancer screening	**Reference**			
Cervical cancer screening up to date				
Age	1.00	0.98	1.03	0.929
Years residing in the US	1.01	0.99	1.04	0.314
Immigration status (US born vs. foreign born)	0.56	0.26	1.23	0.150
Educational Attainment (ref: no schooling)				
Elementary	1.37	0.64	2.93	0.424
Middle school	1.37	0.56	3.40	0.492
High school	2.03	0.88	4.70	0.099
Associate degree	1.24	0.48	3.20	0.663
University degree	1.31	0.50	3.41	0.583
Region of residence (ref: Los Angeles)				
Sacramento	2.57	1.56	4.22	<0.001
San Francisco	3.71	2.05	6.71	<0.001
Insurance Status (ref: no insurance)				
Public	1.06	0.70	1.62	0.776
Private	3.73	1.67	8.34	0.001
English Fluency (ref: monolingual)				
Limited English Use	1.21	0.65	2.28	0.548
Conversational	1.46	0.83	2.55	0.184
Fully Bilingual	0.64	0.29	1.40	0.264
Number of people in the household	1.06	0.96	1.17	0.259
Cervical cancer screening 3 years ago				
Age	1.02	0.98	1.06	0.419
Years residing in the US	1.03	0.99	1.07	0.158
Immigration status (US born vs. foreign born)	0.55	0.17	1.80	0.324
Educational Attainment (ref: no schooling)				
Elementary	1.16	0.30	4.49	0.828
Middle school	2.26	0.51	9.96	0.281
High school	2.82	0.69	11.54	0.150
Associate degree	3.65	0.80	16.73	0.095
University degree	1.41	0.27	7.24	0.683
Region of residence (ref: Los Angeles)				
Sacramento	2.58	1.27	5.26	0.009
San Francisco	3.20	1.32	7.74	0.010
Insurance Status (ref: no insurance)				
Public	0.36	0.19	0.69	0.002
Private	0.77	0.25	2.33	0.638
English Fluency (ref: monolingual)				
Limited English Use	1.25	0.48	3.22	0.645
Conversational	0.86	0.35	2.13	0.747
Fully Bilingual	0.78	0.23	2.57	0.678
Number of people in the household	1.13	0.98	1.30	0.088

*Relative Risk Ratio.

Colorectal cancer screening behavior was statistically significantly different when comparing education attainment, with those with a high school education or higher having 6.4 times the odds of being up to date compared to those with no schooling (P-value 0.001) (Table 6). In addition, living in a houseful with more people was negatively associated with being current with screening (P-value 0.042).

Table 3-6. Multivariate logistic regression model testing the association between colorectal screening behavior and demographic factors among 'Tu Historia Cuenta' participants ages 50+ (N=240, 24 excluded from 264 due to missing data)

Never Colonoscopy as reference	**OR**	**L95%**	**H95%**	**P-Value**
Age	1.04	0.98	1.11	0.165
Years residing in the US	1.00	0.97	1.03	0.882
Immigration status (US born vs. foreign born)	0.98	0.24	3.98	0.980
Educational Attainment (ref: no schooling)				
Less than High School	2.78	1.24	6.47	0.015
High School or more	6.40	2.21	19.37	0.001
Region of residence (ref: Los Angeles)				
Sacramento	1.24	0.52	2.93	0.621
San Francisco	0.99	0.40	2.37	0.974
Insurance Status (ref: no insurance)				
Public	1.24	0.52	2.93	0.621
Private	0.99	0.40	2.37	0.974
English Fluency (ref: monolingual)				
Limited English Use	0.79	0.26	2.54	0.681
Conversational	1.02	0.35	3.14	0.971
Fully Bilingual	1.47	0.39	5.83	0.571
Number of people in the household	0.81	0.66	0.99	0.042

3.3.6 Breast Cancer Family History Survey Results

We used a previously validated family history survey to identify women with strong breast cancer family histories.[155] We obtained a preliminary score and for individuals with scores of 6 or higher, we re-contacted participants to confirm their answers to the survey. THC originally identified 178 participants with a breast cancer family history score of 6 or greater (the 'strong breast cancer family history' category). After confirmation by the promotores, the scores changed as follows: 62 participants maintained a strong breast cancer family history score of 6+, 43 participants moved down to the 'limited family history' category (scores between 2 and 4), and 73 participants moved to the 'no family history' category (score of 0) (Table 7). Reasons for moving categories included: typographical errors when providing answers, answers including distant relatives, confusion between ovarian and cervical cancers, and responses based on other cancer types not linked to breast cancer risk.

Among the participants with a confirmed strong family history score (6+) (N=62), 7 (11.3%) had received genetic counseling before participating in THC, 8 (12.9%) reported having been diagnosed with breast cancer before the age of 50 years, and one woman (1.6%) after the age of 50 years. Among the 43 participants originally identified as 6+ that moved to the 'limited family history' category, 3 (7%) reported a breast cancer diagnosis after age 50 years (Table 7). No participants had breast cancer diagnosed in both breasts. Among participants whose original breast cancer family history score was less than 6, 7 (0.9%) women reported being diagnosed with breast cancer before the age of 50 years, and 4 (0.5%) women after the age of 50 years. Overall, there were 23 participants (2.5%) who reported a personal history of breast cancer, 15 with a diagnosis before the age of 50 years. Follow-up and navigation into genetic counseling and testing for women with a confirmed score of 6+ is currently underway.

Table 3-7. Breast cancer family history score and personal history of breast cancer by post confirmation score, among individuals originally placed in the 'Strong Family History' category

	Original Breast Cancer Family History Score 6+*			**Original Family History Score <6**
New confirmed score	**No Family History (0)**	**Limited Family History (2-4)**	**Strong Family History (6+)**	
	N=73	N=43	N=62	N=756
Received Genetic Counseling prior to THC				
Yes	0 (0.0)	0 (0.0)	7 (11.3)	0 (0.0)
No	73 (100.0)	43 (100.0)	54 (87.1)	756 (100%)
Unsure	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Breast Cancer before 50 (self)				
Yes	0 (0.0)	0 (0.0)	8 (12.9)	7 (0.9)
No	73 (100.0)	43 (100.0)	54 (87.1)	749 (99.1)
Breast Cancer at 50+ (self)				
Yes	0 (0.0)	3 (7.0)	1 (1.6)	4 (0.5)
No	73 (100.0)	40 (93.0)	61 (98.4)	752 (99.5)

3.3.7 Demographic Characteristics by Family History Survey Results

Place of birth and educational attainment both were associated with the breast cancer family history score, with a larger proportion of U.S.-born individuals in the 6+ category (strong breast cancer family history) (15%) compared to foreign-born individuals (6%). Furthermore, the proportion of 6+ score individuals was higher among those with a university degree (16%) compared to women with lower level of educational attainment (4-9%) (Table 8).

Table 3-8. Breast Cancer Family History among 'Tu Historia Cuenta' study participants by demographic variables.

	Family History Score Mean (SD) or N (%)**		
Variable	Strong (6+)	None & Limited (0-4)	P-value
	60 (7)	800 (92)	
Age, years	45.1 (10.1)	42.7 (10.2)	0.09
Year in United States	20.9 (9.9)	18.6 (9.6)	0.12
Place of birth			
Foreign-born*	46 (6)	687 (94)	0.005
US-born	13 (15)	73 (85)	
missing	1 (2)	40 (98)	
English Language Proficiency			
Monolingual Spanish Speaker	9 (6)	152 (94)	0.17
Limited English Use	26 (10)	245 (90)	
Conversational	16 (5)	293 (95)	
Fully Bilingual	9 (8)	106 (92)	
Missing data	0 (0)	4 (100)	
Health Insurance			
No Insurance	23 (7)	303 (93)	0.17
Public	25 (6)	395 (94)	
Private	12 (11)	96 (89)	
Missing data	0 (0)	6 (100)	
Educational Attainment			
No school	3 (5)	55 (95)	0.019
Elementary School	13 (7)	179 (93)	
Middle School	10 (7)	130 (93)	
High School	12 (4)	263 (96)	
Associate Degree	9 (9)	93 (91)	
University	13 (16)	69 (84)	
Missing data	0 (0)	11 (100)	
Number of People in Household	4.2 (1.5)	4.3 (2.0)	0.226

*This includes individuals who were foreign born or moved to the US before 1 year of age

**N=860, which is 31 less than all participants with family history information due to only 860 participants having their family history confirmed up to this time

3.3.8 Feedback Survey

Of the participants, 525 (50.3%) responded to the anonymous feedback survey (Table 9). Most of these participants found the educational materials useful when learning about hereditary breast cancer and stated that they would share the information learned from this workshop with friends and family (97.7% and 94.9%, respectively). Additionally, individuals expressed interest in obtaining more information from their family about their cancer history (93%), and 64.4% responded that they would look for further information on the internet to learn more about breast cancer. Overall, individuals felt comfortable asking questions during the workshop and felt satisfied in the manner that their questions were answered (98.5%, 99.1%, respectively) (Table 9).

Participants were surveyed regarding which topics they found confusing. Half of the participants did not report confusing topics. Thirteen percent of participants reported that they were confused about the concept of the *BRCA*1/2 genes and 7.8% about the increased risk of breast cancer when carrying a *BRCA* mutation. Other concepts covered by the program (e.g., definition of cancer, benign disease, disease stage) were still unclear by the end of the session for 4-5.5% of participants who responded (Table 9).

Table 3-9. 'Tu Historia Cuenta' education session feedback survey responses (N=525)

Question	**N (%)**
Video and discussion were useful to learn about hereditary BC	
Yes	463 (97.7)
Somewhat useful	11 (2.3)
Prior awareness about hereditary genetic risk for BC	
Yes	208 (43.9)
No	266 (56.1)
Will try to obtain more information from family members about cancer history	
Yes	442 (93.2)
No	6 (1.3)
Unsure	26 (5.5)
Will look for information on the internet to learn more about breast cancer	
Yes	302 (64.4)
No	124 (26.4)
Unsure	43 (9.2)
Will share the information learned from this workshop with friends and family	
Yes	445 (94.9)
No	5 (1.1)
Maybe	19 (4.1)
Felt comfortable asking questions during the workshop	
Yes	463 (98.5)
Somewhat comfortable	7 (1.5)
Felt satisfied in the manner questions were answered	
Yes	464 (99.1)
No	3 (0.6)
More or Less	1 (0.2)
The activities conducted during the session were:	
Fundamental	372 (79.5)
Enlightening	90 (19.2)
Unnecessary	6 (1.3)
Concepts that were still confusing after the session	
None	268 (51.0)
Cancer definition	12(4.4)
Difference between benign and malignant tumor	12 (4.4)
Difference between common and hereditary breast cancer	29 (5.5)
Difference between early and advanced stages of breast cancer	21 (4.0)
What a mutation is and how is the mutation hereditary	29 (5.5)
BRCA1/2 Genes	68 (12.9)
Increased risk of breast cancer when there is a BRCA mutation	41 (7.8)
Early detection practices and preventative measures to control BC risk	23 (4.4)

3.4 DISCUSSION

Tools to screen for breast cancer are important to diagnose cases early and improve outcomes.[158] Disparities in breast cancer stage at diagnosis and risk of mortality between H/L and NHW women are partly due to the economic, educational, language, cultural and health care access barriers faced by members of the H/L community.[107, 108] With improvement of genetic screening tools, the H/L community is at risk of being left further behind if programs are not in place to help with access and understanding of these opportunities for prevention.[122, 123]

The goal of this study was to describe the results of a hereditary breast cancer outreach and education program for Spanish-speaking H/L in California and highlight the need for additional efforts to help the community move from awareness and understanding to screening and prevention.

The THC program's target population was Spanish-speaking H/L women in three California cities and surrounding areas (San Francisco, Sacramento, and Los Angeles), who due to their limited English proficiency, socioeconomic and health insurance status, and cultural barriers, might not have access to adequate information and resources for breast cancer prevention, particularly, for prevention of hereditary breast cancer. The demographic characteristics of the program participants were consistent with the target population and supports the crucial role of promotores in connecting with underserved communities. [138, 144, 159, 160]

We limited the program to women older than 21 years of age, and the average age for all participants was 43 years, with some variation by geographic area, with San Francisco participants being younger than those in Los Angeles and Sacramento. The difference in the

average age of participants at the different locations might be a reflection of the age of promotores in the different groups, since the average age of an individual's networks is likely to be concordant with their own age. For programs working with promotores, this may be important as it helps demonstrate that promotores may recruit individuals within their social circles that resemble some of their own characteristics. Having promotores of similar age of the target population of a specific program may be important.

California's Medicaid-managed care legislation established a two-plan model in 14 counties with the largest Medicaid population.[161] Medicaid recipients in these counties can choose between a local initiative and a commercial plan, with the local initiative being the state's effort to help traditional safety net providers compete to retain Medicaid patients. The Los Angeles Care Healthy Plan and the San Francisco Health Plan resulted from this initiative. San Francisco additionally has a program called Healthy San Francisco which provides access to comprehensive health services for uninsured workers and residents of San Francisco.[161, 162] The addition of the comprehensive health care program in San Francisco likely explains why a smaller proportion of individuals were uninsured (9.3%) compared to Los Angeles and Sacramento (44.3% and 44.0%, respectively). The differences in health care access across the cities and the different screening rates observed suggest universal health care may play a role in reducing disparities in cancer screening rates. Additionally, a larger proportion of participants in San Francisco had graduated from high school and had a higher level of English proficiency. Adult immigrants living and working in places where others share their ethnic backgrounds may be less likely to be proficient in English.[163] This may explain some of the differences observed between English proficiency levels as H/L make up 48.6% of the population in Los Angeles, 28.9% in Sacramento and 15.2% in San Francisco. The characteristics of the promotores in the

three cities might also explain the differences in the demographics of participants, even though the promotores had similar educational and linguistic backgrounds.

A study of breast cancer screening among H/L age 40 years and older in San Diego County found that 76.2% of women had received a mammogram in the past 2 years,[164] which is higher than the 56.1% of H/L in our study. This difference may be because 52% of the San Diego County participants had private health insurance and a smaller percent of participants were born outside of the U.S. (76.3%). In addition, our study was conducted during the COVID-19 pandemic which may have affected cancer screening rates.[165] However, other studies have also found rates consistent with what we found. A study including Mexican-American respondents of the California Health Interview Survey (CHIS) found that among women who were uninsured or had no usual source of care and were 40 years and older, 37.8-54.6% reported a mammogram in the past 2 years,[166] which is consistent with the proportion in our study population. Similarly, 73.3% of women in THC were up to date with cervical cancer screening which is within the range reported for Mexican-American women in the CHIS who were uninsured or had no usual source of care (60.0-80.9%).[166] Among the THC participants who were 50 years and older, 23.5% had obtained a colorectal cancer screening; this percentage is lower compared to past studies that identified 50.2-60% of H/L California residents aged 50 years and older who had ever received colorectal cancer screening[167, 168] but is similar to findings from a Northern California catchment area population assessment.[169]

The THC participants who had never obtained a mammogram reported a higher average number of household members, which is a measure that correlates with socioeconomic status, thereby suggesting that participants who never had a mammogram within the THC study may also be those in the lowest income bracket.

Participants expressed interest in learning about hereditary breast cancer and genetics despite limited knowledge at the time of registration. The proportion of participants identified as having strong family history of breast cancer (~7%), is concordant with other estimates in studies assessing breast cancer family history in unaffected women.[170-172] The larger proportion of women with a high breast cancer family history score among U.S.-born (15%) compared to foreign-born participants (6%) might be due to differences in the flow of information about cancer family history in these two groups. A similar interpretation can be posed for the higher proportion of women with university degrees with strong breast cancer family history. Comparing the rate of high penetrance mutations by place of birth and reported family history of cancer could provide important information about the carrier status predictive accuracy of the breast cancer family history survey by immigration status/generation among H/L in California.

There were 116 individuals whose breast cancer family history survey scores changed after a second conversation with promotores. Over-reporting of cancer family history has been noted in previous studies.[173, 174] The most common reasons for the discordance between the original survey response and that after a second contact were unintentional errors when choosing options and confusion about type of cancer in the family (e.g., ovarian vs. cervical, which has been previously described[175]). Only participants who had initially had a high family history score (greater than or equal to 6) were part of the confirmation group, which could lead to underestimation of the proportion of participants in the strong family history category.

A strength of this study was that we were able to connect to a population that is often excluded from health studies (35.8% of the study participants did not have health insurance and ~48% were either monolingual Spanish-speakers or had limited English proficiency). Another strength was that researchers worked closely with promotores to ensure the relevance and

accessibility of the study materials and process, while engaging community members to obtain their perspective and perceptions of the program.[148] Due to the pandemic, all the education sessions were held virtually. Hosting sessions virtually allowed more women to participate, as usual barriers for in person education were removed (e.g., transportation, child and elderly care responsibilities).

The study has some limitations. Participants were enrolled through the work of two organizations and individuals were recruited from promotores' social circles and networks. Consequently, results from this study may not be generalizable to the overall population of Spanish-speaking H/L in San Francisco, Sacramento, and Los Angeles County. Additionally, the education program advertised learning about hereditary breast cancer, which could have influenced people to participate if they had a personal interest based on their family history of cancer. However, the percentage of individuals in the THC study identified as candidates for genetic counseling (7%) was slightly less than what has been reported for the general population of unaffected women in the U.S. (8% to 12%),[170-172] suggesting that the study sample is not enriched for people with strong family history of breast cancer.

Overall, participants found the THC education session to be useful, and most of the participants reported willingness to share the information they acquired in the session with their friends and family. We hope the sharing of information will lead to greater awareness about hereditary breast cancer in California Spanish-speaking H/L communities.

3.5 CONCLUSION

The THC promotores-led outreach, education and breast cancer family history assessment program implemented in San Francisco, Sacramento, and Los Angeles in June 2020

has reached more than 1000 Spanish-speaking H/L. Since then, we have identified 62 women (7%) which based on survey responses could benefit from genetic counseling, 272 (42.8%) women due for mammograms (64 of whom we have navigated to the EWC program), 250 (24.7%) due for Papanicolaou test, and 189 (71.6%) due for colorectal cancer screening. Follow-up of the THC participants who were referred to and/or navigated to genetic counseling and testing will be important to assess the long-term impact of the program on the prevention of advanced breast cancer diagnosis among Spanish-speaking H/L with strong family history of the disease.

The results from the THC study highlight the need for additional programs targeted to this underserved population in order to spread awareness about cancer risk and facilitate access to resources for prevention.

Chapter 4 CONCLUSIONS AND FUTURE DIRECTIONS

4.1 CONCLUSIONS

In this dissertation, we investigated various aspects of arsenic metabolism, genetic susceptibility, and breast cancer screening in specific populations. The findings from each chapter provide valuable insights into the complexities of these topics and underscore the need for further research and targeted interventions.

In Chapter 1, our GWAS analysis of arsenic species in urine and blood of arsenic-exposed individuals in Bangladesh revealed both shared and distinct genetic effects on different arsenic species. We identified associations between specific genetic variants (*AS3MT* and *FTCD* SNPs) and arsenic metabolism efficiency, as well as an unexpected involvement of FMO genes in arsenic metabolism. These findings suggest the presence of complex mechanisms underlying arsenic metabolism, distribution, and elimination that warrant further investigation. The differential associations between genetic variants and arsenic species highlight the need to consider the toxicokinetic impacts of specific variants on different forms of arsenic. Furthermore, our study emphasizes the importance of population-specific investigations to unravel the complexities of arsenic metabolism and toxicity.

In Chapter 2 focused on an intervention study that involved returning genetic results on arsenic susceptibility to Bangladeshi research participants with a history of high arsenic exposure. Our findings indicated that participants who received genetic results were motivated to reduce their arsenic exposure. While there was an overall reduction in urine arsenic levels across all study arms, the reduction was not statistically different between the intervention and control arms. This suggests that the one-on-one informational intervention, which provided participants

with information on the health effects of arsenic exposure and the importance of well-switching, was effective in reducing arsenic exposure. The high participation retention rate and positive feedback from participants highlight the value of providing genetic information to high-risk individuals in low-resource settings. However, longer-term studies are needed to assess the sustained impact of returning genetic results on health behaviors and outcomes. As the state of the science moves towards an era of personalized interventions, this chapter serves as an important milestone in integrating genetic susceptibility into practical health strategies.

In Chapter 3, we described the results of a hereditary breast cancer outreach and education program for Spanish-speaking Hispanic/Latino (H/L) populations in California. The program targeted individuals who faced barriers to accessing information and resources for breast cancer prevention, particularly hereditary breast cancer. The demographic characteristics of the program participants were consistent with the target population, emphasizing the crucial role of promotores in connecting with underserved communities. Our study highlighted the disparities in breast cancer screening rates and the need for additional efforts to move beyond awareness and understanding to screening and prevention in the H/L community. The program's success in reaching and engaging the target population demonstrates the importance of tailored outreach, education, and support programs for improving cancer prevention and early detection in underserved communities.

4.2 FUTURE DIRECTIONS

Future research endeavors should continue to delve into the intricate mechanisms governing arsenic metabolism, with a particular emphasis on the dynamic interplay between genetic variants and environmental factors. Building upon the foundation laid by this study

(Chapter 1), efforts to validate the identified genetic associations across diverse populations with varying arsenic exposure levels are imperative. The evolving field of toxicogenomics and advancements in molecular techniques offer promising avenues to uncover the functional significance of genetic variants, such as *AS3MT, FTCD, FMO3,* and *GSTO1,* in arsenic toxicity. Integrating cutting-edge methods, such as single-cell sequencing and metabolomics, could provide unprecedented insights into cellular responses to arsenic and further elucidate the role of genetic susceptibility. By employing multi-omics approaches, future studies can bridge the gap between genetic predisposition and arsenic-induced health outcomes, thereby paving the way for targeted interventions tailored to individuals' genetic susceptibilities.

In light of the burgeoning field of personalized medicine and the increasing availability of genetic testing, future investigations should expand upon the outcomes of this intervention study (Chapter 2). Given the nuances of genetic susceptibility and the diverse sociodemographic landscape, exploring the differential effects of genetic results on various subgroups within arsenic-exposed populations is paramount. Incorporating advancements in behavioral psychology and health communication, researchers can design interventions that effectively address psychological and emotional responses to genetic susceptibility information. Longitudinal studies that span extended periods are essential to comprehensively assess the lasting impact of genetic susceptibility-informed interventions on health behaviors, outcomes, and ultimately, arsenic-related health risks. The integration of wearable health technologies and mobile applications may further enhance the personalized nature of interventions, fostering sustained engagement and behavior change among high-risk individuals.

Continuing to advance the field of community-based interventions for hereditary cancers necessitates an expansion beyond breast cancer and a broader focus on diverse underserved

populations. Informed by the success of the "Tu Historia Cuenta" program (Chapter 3), future efforts should encompass a spectrum of hereditary cancers, leveraging genetic susceptibility insights to tailor outreach, education, and early detection initiatives. Collaborations between researchers, healthcare institutions, and policymakers are pivotal in scaling up community-based programs, ensuring widespread accessibility and sustainability. Building upon the momentum generated by our study, it is crucial to investigate innovative ways to overcome systemic barriers to cancer screening services. Integrating telegenetics and telemedicine into community-based interventions may circumvent access limitations and empower underserved populations to harness genetic susceptibility information for informed decision-making. By extending the reach of tailored interventions and reducing disparities, future research can usher in a new era of equity-driven cancer prevention strategies.

In conclusion, these future directions build upon this dissertation's foundational work, intertwining genetic susceptibility and interventions within the framework of advancing science. As the field of genomics and personalized medicine continues to evolve, the contributions made by this dissertation can help contribute to the development of targeted strategies to mitigate the health risks associated with arsenic exposure and improve cancer outcomes in underserved populations.

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