Medical Distrust in Applied Genomic Sequencing: Prediction, Perceptions, and Patient outcomes

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Abstract

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Background: A growing collection of research shows medical distrust negatively impacts a wide range of health behaviors and outcomes including: rates of preventive screening, treatment adherence, and satisfaction with care. Despite evidence suggesting medical distrust may impact genomic sequencing research participation, limited work has been conducted to explore who may be affected by medical distrust and how health outcomes associated with genomic sequencing are impacted.

Objective: The goal of this work is to: 1) Identify a prevalence estimate and predictors of medical distrust in a clinical research sample of adults undergoing exome sequencing to diagnose hereditary cancer syndromes. 2) Analyze the impact of medical distrust on patient perceptions of

utility and feelings associated with the receipt of genetic results. 3) Assess the impact of medical distrust on the uptake of recommended care and patient-initiated health behavior changes as well as willingness to share genetic information with health care providers and family members.

Methods: Data for these analyses was collected as part of the Cancer Health Assessment Reaching Many (CHARM) project conducted by Kaiser Permanente Northwest (KPNW). This project targets AHRQ priority populations in a multi-site implementation study of clinical exome sequencing for heredity risk of cancer syndromes and includes a nested treatment arm testing literacy-focused genetic counseling tailored to low health literacy populations. Participants were recruited based on their familial history of cancer though in-clinic contact and via text messages and email. Measures were collected in-clinic via tablet using web-based surveys during the baseline timepoint and submitted online during two subsequent timepoints.

Analyses: Prevalence estimates were assessed using cut points from previous literature on medical distrust. We used three models of prediction selection to determine predictive patient-level characteristics: backward stepwise regression and two least absolute shrinkage and selection operator model, varying the level of conservativeness of selection. To analyze the relationship between distrust and patient reports of utility and feelings associated with return of genetic test results we used linear multivariable modeling. A final multiple logistic regression was used to assess the impact health care system distrust has on the likelihood patients adopt recommended health behavior changes based on genomic test results and whether patients share those results with family members and providers.

Results: The point prevalence estimate showed medical distrust to be as present in a medical genomic research context (32%) as it is in other medical contexts. African American race/ethnicity, poor access to health care, transgendered/non-binary gender identity, worse

mental health status, lower income and higher education predicted high medical distrust. We found no impact of medical distrust on feelings related to the return of genomic results there was, however, a negative relationship between medical distrust and perceptions of utility of genomic results. There was inadequate data to analyze an effect between medical distrust and following medically recommended advice. Personal health behavior change based on genomic results were not impacted by level of medical distrust. Higher medical distrust was related to lower odds of sharing genomic results with family members, but no relationship between medical distrust and discussing results with health care provider was observed.

Discussion: Patient socio-demographic, health status, and access to health care variables predict medical distrust. While medical distrust may not impact feelings related to receipt of medical results, it seems to lower the perceived utility of genomic sequencing. This may illustrate a mechanism by which medical distrust discourages positive health behaviors. The negative impact of medical distrust on familial information sharing undermines a unique benefit of genomic medicine. However, the lack of association between medical distrust and personal health behavior change and discussion of results with health providers may indicate that information gained from genomic sequencing could be especially resilient to the negative impacts of medical distrust.

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DEDICATION

I would like to dedicate this work to my family. My wife Michelle Lindsey Mcintosh, whose example encourages me to direct my work and my life towards love, compassion, and equity. My daughters Miriam Juniper Angelo, and Olive Celeste Angelo who taught me to be a father and continue to teach me how to be a better one. My parents, Dana and Myralee Angelo, Karin and Robert Mendell, and Greg and Claudia Mcintosh who's values I carry forward. Finally, to my dog, Teddy, who is a very good boy.

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Chapter 1. Introduction

1.1 Background

Researchers have long acknowledged trust between patients and health care providers is essential to realize the benefits of health care.[1] Rapidly evolving models of care provision and administration have added layers of complexity to when, where, and how patients interact with their care providers. In this context, interest in evaluating the impact of changes in practice on patient-provider trust grew.[2] The Trust In Physician Scale (TIPS) was developed to assess patient trust, defined as "*the belief that a trustee (the provider) will act in the best interest of the patient.*"[3]

Research findings generated by the TIPS confirmed the supposition that trust between patients and providers is important to patients' wellbeing. Higher levels of trust were related to better adherence to treatment [4] and chronic disease management [5], higher levels of health information disclosure and better access to care[6], and greater patient satisfaction with care.[7] Trust in physicians, and the benefits it imparted, were observed at a roughly equal rate in both majority, and marginalized communities. Despite parity in trust in physician between marginalized and non-marginalized communities, disparities still existed in health outcomes and research participation between African American populations and their white counterparts.

Qualitative investigation of rates of research participation began to shed light on the differences in trust relationships between marginalized and non-marginalized populations. While patients of color were just as likely as white patients to trust their own physician, researchers observed concerns about personal safety and autonomy with the wider medical establishment.[8,9]

This dynamic allowed the differences in medical trust beliefs to go undetected for a decade. Assessments of medical distrust, typically defined as "*the belief that a trustee (health care provider) will act against the best interests of a patient*", were developed to draw a distinction between what had been observed with the TIPS and what qualitative researchers were hearing from participants. The construct of medical distrust was defined as directly opposite of medical trust, but there is another important distinction to attend to. Assessments of distrust typically use a more diffuse referent than trust. While the TIPS asked about "*your doctor*", assessments of medical distrust use referents such as "*doctors and medical professionals*"[10], "*the health care system*"[11], and "*health care organizations.*"[12]

Medical distrust is a demonstrable barrier to care. Research has found associations between medical distrust and lower rates of medication adherence, lower follow-through on recommended cancer screenings,[13-15] neglect of medical advice, missed follow-up appointments, delay of recommended care, lower satisfaction with care,[16] lower self-reported global health, [17-19] and poorer quality of life.[20] Medical distrust and the negative impacts that come with it are consistently more prevalent in racial/ethnic minority and medically underserved populations.[21-24] Recent evidence suggests that distrust has a stronger and more reliable association with health behavior change than does trust.[25,26] Phrased differently, trust is necessary, but not sufficient to reliably predict behavior change while distrust is typically sufficient to prevent behavior change. Given the impact medical system distrust has on health and health behavior, more attention should be given to this topic.

1.2 Conceptual model of medical distrust

This research is driven by the conceptual model in figure 1.1. This conceptual model was adapted from Armstrong and colleagues' Conceptual Model of Health Care Distrust,[19] with

additional influence from the Health Belief Model of health behavior change.[27,28] Our model posits that medical distrust is a cognitive bias, or heuristic, that influences the experience of the clinical encounter, information uptake, and decision making. These biases are taken into the clinical encounter where patients receive medical information including diagnosis, risk assessment, and treatment recommendations. After the encounter, cognitive bias, interact with perceptions and emotions related to the clinical encounter, recommended treatments, and information gained to form an Affective-cognitive appraisal of the medical recommendations. This step represents decision making process where patients weigh information, biases, emotional response, and perceptions to decide whether they will adhere to medical recommendations or change health behavior. It is assumed that the adoption or resistance to heath behavior change will ultimately influences health outcomes. A distinction is drawn between biases, and perceptions in this model. Biases or beliefs, exist prior to the clinical encounter and are thought to be more rigid and less vulnerable to influence. Perceptions may come from the clinical encounter itself or arrive from wider cultural opinions about care and are more malleable than biases.[27,28]

1.3 Medical Distrust and Clinical Genomic Sequencing

The benefits of clinical genomic sequencing are realized through the identification of heritable disease risk that can inform prevention and treatment decision making. These benefits are gained only after sequencing results are discussed with medical providers and subsequent medical recommendations are engaged with and adhered to. If the impact of medical system distrust in genetic medicine is analogous to its impact in other medical contexts it may directly undermine benefits patients receive from clinical sequencing by limiting results disclosure and treatment adherence. Despite these previous findings, research investigating medical distrust in

the applied genetic sequencing context is sparse, focusing primarily on its negative impact on research participation.[21-24,29,30] In the clinical sequencing literature, medical distrust is implicated as the primary reason for refusal to participate in medical research by minority adults.[24,29,31-33] While this is unsurprising based on historical wrongdoings perpetrated on vulnerable populations in the name of medical research, underrepresentation of racial and ethnic minority adults reduces generalizability of findings and perpetuates race-based disparities. This is especially true in genomic medicine where a diverse and broad range of genomic samples (often tens-of-thousands) is needed to find reliable links between genes and disease traits. These links, known as Genome Wide Associations (GWAs), are found by mapping complete sets of DNA to gene variants associated with particular disease factors or physiological responses to medications. The lack of research participation of racial/ethnic minority adults reduces many important opportunities for discovery: population specific disease markers, evidence relevant to differential drug efficacy by population, and generalization of previous GWAs findings from other populations. [34-37] This limits options for screening, treatment, and prevention.

Information about heritable disease risk is unique because this information can be shared amongst family members allowing family-wide health benefits. This information represents a valuable tool to inform family members about the risks of heritable disease and the importance of screening or other forms of medical engagement. Familial sharing of health information and recommendations for screening or treatment is particularly influential among Latinx and African American families.[38-42] Based on previous findings showing lower trust is associated with lower medical disclosure, this added benefit may be vulnerable to the negative impact of medical distrust.

Currently, no prevalence estimates of medical system distrust exist in research populations willing to undergo clinically indicated sequencing, nor has medical system distrust been examined for its potential impact on patients' perceptions of sequencing, adherence to medically recommended behavior changes or willingness to share genetic information with family members and providers.

1.4 Specific aims

The three studies that comprise this dissertation use the conceptual model presented above to evaluate the prevalence, predictors, mechanisms of impact, and behavioral outcomes associated medical distrust in a medical genomics research context.

1.4.1 *Specific aim 1*

Specific Aim 1: Identify prevalence estimates and patient-level predictors of medical distrust. Study 1 uses survey data to generate a point-prevalence estimate of medical distrust. It then uses the same data along with patient-level socio-demographic, health care access, and health status to predict high medial mistrust in this sample. Three competing models of prediction were generated utilizing backward-stepwise logistic regression, and two different least absolute shrinkage and selection operator models that varied in conservativeness for variable selection criteria. A model was chosen based on goodness-of-fit measures selected a priori. Marginal mean analysis was then conducted on continuous and ordinal patient-level variables selected by the prediction model to highlight the strength and directionality of its relationship to the probability of high medical mistrust.

1.4.2 *Specific aim 2*

Specific Aim 2: Examine the relationship between health care system distrust and Affective-cognitive appraisals: perceptions of personal utility and emotional responses to genomic test results. Study two uses survey data to assess the impact of medical distrust on perceptions of the personal (non-clinical) utility of genomic sequencing results, and feelings associated with receipt of genomic results. Linear regression was used to evaluate possible associations between medical distrust and the multiple domains included in both the personal utility survey and the survey of feelings related to receipt of genomic results.

1.4.3 *Specific aim 3*

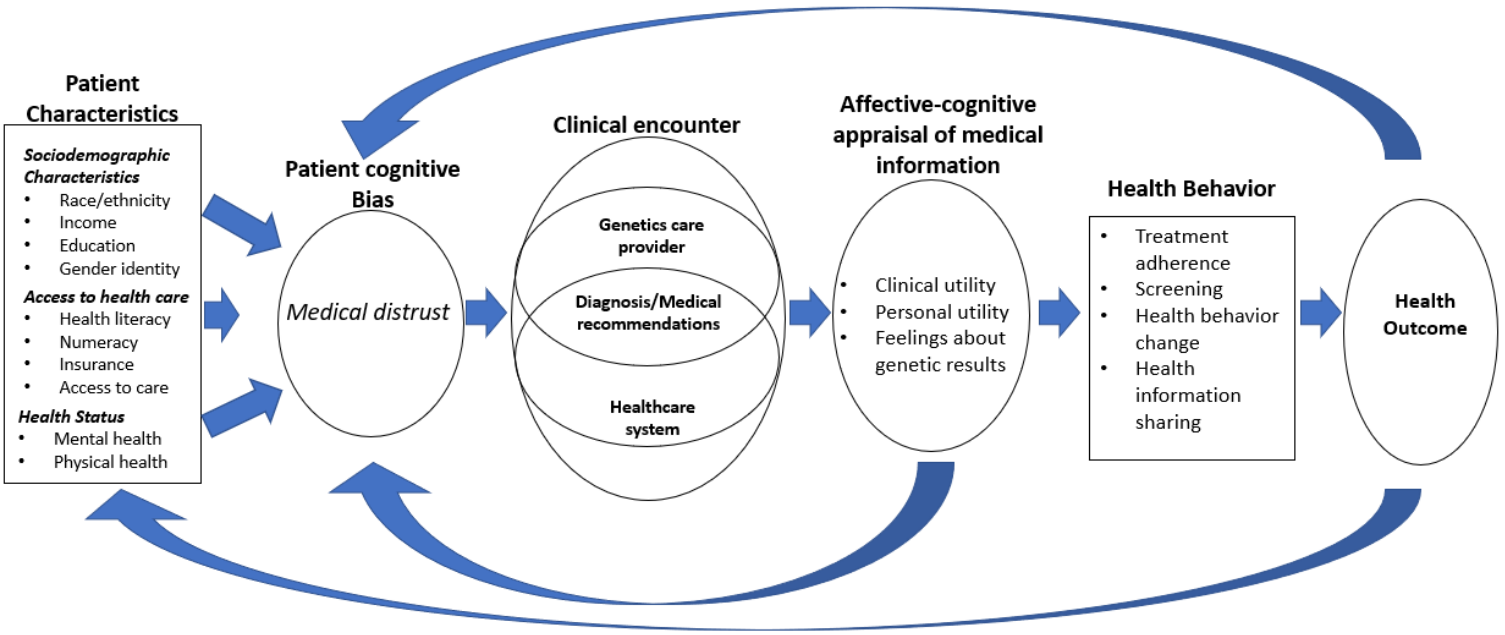
Specific Aim 3: A) Evaluate the relationship between health care system distrust and patient-initiated and medically indicated health behavior change after receipt of results.

B) Investigate the relationship between health care system distrust and sharing of genetic results with family members and medical providers. Study 3 examined the impact of medical distrust on multiple self-reported heath behavior endpoints. Aim 3A utilized a novel survey item to assess self-reported intentions to change personal health behavior related to genomic results, but not recommended by a health care provider, and intent to change heath behaviors based on health care provider recommendations. We used logistic regression to examine the relationship between the intentions to change health behavior and high medical distrust. If a relationship is observed between medical distrust and intent to change heath behavior, the possibility of mediation by personal utility beliefs and feelings associated with receipt of medical results was explored. Aim 3B, utilized novel items to assess intent to discuss genomic information with providers and with other family members. We assessed the relationship between medical distrust between intent to share information genomic with providers and with family members using logistic regression

models. If the models showed statistical significance, the relationship was assessed for mediation by perceived utility and feelings related to receipt of genomic sequencing results.

The current study focused recruitment on racial/ethnic minority populations who might not otherwise participate in genomic research and provides clinically indicated sequencing to screen for genetic cancer syndromes. This is an improvement over previous work, which often relied on predominately Caucasian populations and samples that may or may not receive sequencing. Utilizing research participants who are willing to undergo genomic sequencing provides us insight from a sample similar to those clinicians are most likely to encounter during practice. These findings give us insight into the prevalence and patient level predictors of medical distrust in clinical samples receiving exome sequencing, its impacts on perceptions of sequencing information, and its effect on compliance with recommended health-behavior changes and information sharing. Ultimately, modeling distrust may give us information on how and when clinicians can target and successfully apply existing strategies of evidence-based interventions for health behavior and attitudinal change such as motivational interviewing or contingency management to address its negative impacts.

Figure 1.1 Conceptual model of medical distrust



Chapter 2. Prevalence and Prediction of Medical Distrust in a Diverse Medical Genomic Research Sample

2.1 Abstract

Purpose: Medical distrust has been identified as a persistent barrier to medical care, impacting preventative screening, treatment uptake and adherence. Despite this, little research to date has examined medical mistrust in a genomic medicine context. The goal of this work is to assess the prevalence of medical distrust in a genomic medicine research study and examine patient-level demographic, access-related, and health-status related characteristics that predict medical distrust.

Methods: We assessed medical distrust in a research sample of adults (N=967) receiving genomic sequencing to screen for heredity risk of cancer syndromes in the US. We utilized multiple predictive variable selection models to determine predictors of medical distrust followed by marginal mean analyses to characterize the relationships.

Results: The prevalence of medical distrust was 32%. The final stepwise model indicated Black/African American race/ethnicity, trans, non-binary, or non-identifying gender identity, high education, low income, low access to health care, and poor SF-12 mental health composite scores predict medical distrust.

Conclusion: Medical distrust may pose similar challenges to genomic sequencing as it does in other medical contexts. The pattern of variables that predict distrust suggest increasing access and accommodation for stigmatized and underserved communities may help overcome the negative effects of medical distrust.

2.2 Introduction

Medical distrust, the belief that the medical system may act contrary to patients' interests[43], has historically been considered the opposite of trust with regard to its impact on health behaviors and outcomes. However, evidence suggests that distrust is more strongly and more reliably associated with health behavior than is trust.[25,26] Phrased differently, trust is necessary, but is not sufficient to reliably predict health behavior while distrust is typically sufficient to predict health behavior. A demonstrable barrier to care, medical distrust negatively impacts multiple health-related patient behaviors and outcomes across many medical contexts. Researchers have found medical distrust is associated with lower rates of medication adherence, lower follow-through on recommended cancer screenings,[15,44,45] neglect of medical advice, missed follow-up appointments, delays in receipt of recommended care, lower satisfaction with care,[46] lower self-reported global health,[17,18] and poorer quality of life.[20] Medical distrust is consistently more prevalent in racial/ethnic minority and medically underserved populations.[21-24]

Little is known about the impact of medical distrust on outcomes associated with genomic medicine. Much of the benefit of genomic sequencing is realized through the identification of heritable disease risk that can inform prevention and treatment decision making. These benefits are gained after patients engage with and adhere to follow-on medical recommendations. If the impact of medical distrust in genomic medicine is analogous to its impact in other medical contexts, medical distrust would directly undermine benefits patients receive from genomic sequencing. Despite these risks, research investigating the impact of medical distrust in the applied genomic sequencing context is sparse, focusing primarily on its negative impact on research participation.[21,23,24] Currently, no prevalence estimates of medical distrust exist in populations willing to undergo genomic sequencing to identify clinically actionable genetic conditions, which is the sample clinicians are most likely to encounter. Moreover, given the impact of medical distrust on health behavior, we should strive for a better understanding of what characteristics increase vulnerability to the negative impact of distrust.

A conceptual framework of medical distrust was put forward in Armstrong et al., (2006) suggesting prior experiences, and socio-demographic, cultural, and personality traits predict medical

distrust.[19] Their model treats health status and access to medical care as a product of medical distrust. There is a possibility, based on the reliability of association in the literature, that these patient-level characteristics are drivers of mistrust mistrust.[17,18,46,47]

The objective of this retrospective cohort study was two-fold. First, we estimated the prevalence of healthcare system distrust in a diverse research population who agreed to receive genomic sequencing to identify risk of heritable cancer syndromes. Second, we compared the three separate methods of predictive modeling to develop the strongest predictive model of medical distrust using patient-level sociodemographic variables, health care access-related variables, and health-status variables and examined the strength of predictor-outcome associations.

2.3 methods

2.3.1 *Conceptual framework*

We used a conceptual framework adapted from Armstrong et al., (2006) to guide this research. (figure 1.1).[19] Our model expands on their original model with the addition of access to medical care and health status variables as predictors of cognitive biases, in this case medical distrust. Cognitive biases enter the clinical encounter and is affected by both the behavior of the health care provider and treatment environment. After receiving sequencing results, patients use their cognitive biases to appraise the utility of both the sequencing results and the medically recommended behavior changes advised by their care provider. Health behavior change decisions are made and then acted upon ultimately impacting health status.

2.3.2 *Data Source*

Data used for these analyses were collected as part of the Cancer Health Assessment Reaching Many (CHARM) study. The CHARM investigation had multiple goals, including implementation of hereditary cancer risk assessment, tailoring critical interactions for diverse populations, evaluating the personal and clinical utility of exome sequencing in the clinical context, and addressing barriers of

implementation of genomic sequencing into clinical decision-making. The Aims and methods used by the CHARM study are described in greater detail elsewhere.[48] CHARM is part of the larger Clinical Sequencing Evidence-Generating Research (CSER) consortium comprised of seven individual RO1 level research projects.[49] To meet eligibility criteria to enter the CHARM study, patients were required to have screened at high-risk on the Probe Empower Manifest Lynch syndrome screening tool[50], moderate to high-risk on the Brest Cancer Genetics Referral Screening Tool [51], or had limited or unknown family history of cancer and Lynch syndrome. Recruitment was focused on clinic sites that provide care to highly diverse populations, specifically the Rockwood, North Lancaster and Gateway clinics within the Kaiser Permanente Northwest system, and Denver Health, a FQHC located in Denver County with 9-sites. Study staff recruited participants in-person, in-clinic when possible, otherwise they used postal and electronic messaging. After recruitment, patients completed a battery of survey measures and provided a biological sample for exome sequencing to screen for heritable cancer risk. Study staff enrolled 842 adults, aged 18-50, across the two years of active recruitment. Randomization to differing genetics counseling arms and additional follow-up time points were part of the larger CHARM study protocol, however, the current analysis focuses exclusively on data collected at the baseline timepoint.

2.3.3 *Outcome Variable*

We assessed medical distrust with the Revised Health Care System Distrust Scale (HCSD).[52] This and previous versions of the HCSD have been psychometrically validated and used in many peer reviewed articles.[19,43] We chose the HCSD for this investigation because it is considered a "gold standard" in medical distrust assessment and does not focus on a specific referent for the medical distrust (physician, insurer, hospital, group membership).[26] We utilized HCSD scores in two ways for these analyses: 1) to assess prevalence of distrust in this sample and 2) as the outcome for the predictor analyses.

2.3.4 *Predictor Variables*

We identified potential patient-level associations and predictors for our prediction models based on previous medical trust and distrust literature.[12,19,47,53,54] These variables were organized conceptually into three categories: sociodemographic variables, health status, and health care access-related variables. The sociodemographic variables consisted of age in years, self-reported race/ethnicity (American Indian/Native American/Native Alaskan, Black/African American, Asian/ Pacific Islander, Hispanic/Latino, White/European American, Middle Eastern) of which patients were allowed to select multiple categories, yearly income, highest education level, and gender identity. Gender identity included options: male, female, and transgender and non-binary/non-identifying identities. Physical and mental We assessed health status using the Mental Component Score (MCS) and Physical Component Score (PCS) of the Short Form 12 (SF-12)[55] Health care access-related variables included the validated BRIEF health literacy scale[56] and the Short Numeracy Scale-3 (SNS-3),.[57] The CSER consortium researchers developed a number of novel items for circumstances when existing measures were inadequate. This included an insurance status question, asking "Are you covered by health insurance or some other kind of health care plan? (Include health insurance obtained through employment or purchased directly as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills)" An additional novel item assessed health care access, asking "Has there been any time in the last 12 months when you wanted or needed to see a doctor or health care professional and did not?" Patients answered this item "yes" or "no".

2.3.5 *Statistical Analysis*

The HCSD is a 9-item scale rated via Likert scoring (1-5), generating a total score range between 9 and 45, with higher scores indicating greater levels of medical distrust. We coded medical distrust differently for the prevalence estimates and prediction modeling. We established prevalence estimates of medical distrust using cut points established by Gupta et al, 2014.[47] These cut points determined medical distrust as a score between 28 and 45 on the HCSD and were coded 1 if the patients met this criteria, 0 if they did not.[47] This was done to facilitate comparison of our prevalence estimate to previously existing

prevalence estimates in other medical context. For prediction modeling of medical distrust, we used highest quartile HCSD score (32 to 45 in this sample) to indicate medical distrust. The HCSD highest quartile score was dichotomized such that patients received a score of 1 if their score fell within the highest quartile, and a 0 if they did not.

Predictor variables were coded as follows. Age in years was treated as a continuous variable. Self-reported racial/ethnic category, coded 0= not a member, 1= member. Yearly income was ordinally coded, 1 through 7, from $0 to $140,000+ in $20,000 increments. Education was also ordinally coded, from 1 to 4 (high school education or less, post-high school training or associate degree/certificate, Bachelor's degree, graduate or professional degree) with higher scores indicating more education. The SF-12 version 2 MCS and PCS were generated using the recommended scoring paradigm.[55] The SF-12 composite scores are normed against population data to zero, with scores lower than zero indicating poorer mental and physical health, and scores above zero representing better mental and physical health. These items were treated as continuous. The BRIEF Health literacy scale consisted of 4- items and was scored on a 1 to 5 Likert scale with higher scores are associated with greater health literacy.[56] The SNS-3 numeracy scale was three item, scored on a 1 to 6 with higher scores associated with greater numeracy.[58] The novel insurance status question, low health care access, and native English speaker status were coded dichotomously, with 1= yes, and 0 = no.

To examine the predictive ability of the independent variables on membership in the highest quartile of HCSD scores we created three competing models and chose the strongest based on our selection criteria listed below. We began by developing a backward stepwise logistic regression model. We set the p-value for variable selection into this model to .10, which allows the model greater leeway in selecting variables that generate the best fit. We created two additional least absolute shrinkage and selection operator (LASSO) models. The first model was more conservative than the second and used a lambda tuning parameter to minimize mean square predicted error as selection criteria.[59] We refer to this model as LASSO MSPE. The second, less conservative method, used a lambda tuning parameter that

choses the lambda value in which the mean squared predicted error is within one standard error (OSE) of the minimal mean squared predictive error.[60] We refer to this model as LASSO OSE. These three models offer multiple methods for variable selection at differing levels of conservativeness and selection criteria.

The selection models were validated using 10-fold cross validation to guard against over fitting to the sample. We compared all three models for best fit, using Akaike Information Criterion divided by number of participants (AIC/N), Bayesian information criterion (BIC), mean $R^2_{Mcfadden}$ values estimated using 10-cross validation, and finally a Receiver Operator Curve (ROC). We performed multiple post-hoc marginal mean analyses to examine the strength and direction between significant continuous and ordinal predictor variables and the probability of being in the highest quartile HCSD scores using the final selected prediction model to examine probability and directionality of the relationships. We conducted all analyses using STATA 14[61]; the Stata module CROSSFOLD was used for the k-fold cross validation.[60] Research was conducted in compliance with the University of Washington Internal Review Board, who deemed this de-identified data set for secondary analysis to be non-human subjects research.

2.3 Results

Of the 967 patients consented, 815 completed the HCSD and were included in these analyses. This sample was predominantly female (76.34%) with a mean age of 36.02 (8.24) years. Self-reported race/ethnicity included 53% White/European Americans and 46% and racial/ethnic minorities. Hispanic/Latino(a) representing the largest proportion of the racial/ethnic minority cohort at approximately 34%. (Table 2.1) The prevalence of medical distrust in the overall sample was 32%, and higher in transgender and non-binary/non-identifying adults (64%), Black/African American adults (43%), and multi-racial adults (42%). The lowest prevalence of medical distrust was seen in Hispanic/Latino adults (26%) (table 2.2).

There was overlap in the variables selected by each of the three predictive models (Table 2.3). The LASSO MSPE model selected gender, education, low health care access, and SF-12 MCS. The

backward stepwise logistic regression model added African American race/ethnicity, and yearly income. The less restrictive LASSO OSE model favored dropping the yearly Income variable. Looking at the AIC/N and BIC selection criteria, all three models scored similarly, but slightly favored the backward stepwise model. The backward stepwise model also had the highest mean $R^2_{Mcfadden}$ after 10-fold cross validation. The area under the curve scores (AUC) of the ROC analyses, were again close, but still favored the stepwise model, with LASSO MSPE AUC=0.69, LASSO OSE at AUC=0.70, and the stepwise model with an AUC= 0.72. (Figure 2.1) All selection criteria indicated the stepwise predication model had the best fit amongst the three models attempted.

The final stepwise model indicated Black/African American racial/ethnic status, transgender and non-binary/non-identifying gendered adults, higher education, lower income, low health care access in the last year, and poorer mental health status are predictive of being in the highest quartile of HCSD scores in this population (Table 2.4). For the significant continuous and ordinal predictor variables we estimated marginal means to characterize the relationship between the variable and the likelihood of highest quartile HCSD score. (Figures 2.2, 2.3, 2.4, and 2.5). Lower mental health status scores, particularly scores below the normed value of 0 for the population average, are associated with greater probability of highest quartile HCSD score. (Figure 2.2) Higher education levels are associated with greater probability of highest quartile HCSD score. (Figure 2.3) Examining the marginal means of the effect of income on the on highest quartile HCSD scores reveal a clear pattern of relationship between lower income and highest HCSD quartile probability. (Figure 2.4) A final marginal mean comparison examining the relationship between education and probability of highest HCSD quartile score but separated the results by income level (Figure 2.5) suggests the highest educated individuals with the lowest income levels had the greatest probability of HCSD highest quartile scores.

2.4 Discussion

We found a 32% prevalence of medical distrust in our diverse population of clinical genomics research participants. After constructed multiple competing models to predict the probability of highest

quartile medical distrust scores, the best model included all three types of variables – sociodemographic, health status, and health care access. Our results suggest transgender and non-binary/non-identifying gender identity, Black/African American race/ethnic identity, higher education, lower income, poorer mental health, and difficulty accessing health care in the previous year were the most influential predictors of medical distrust.

Estimates of the prevalence of medical mistrust in clinical research are extremely limited. Our estimate of 32% prevalence of medical mistrust is similar to the prevalence of distrust found in Gupta 2014, who observed a 35% prevalence of medical distrust in a clinical research sample of patients who were hospitalized for cardiac issues.[47] This suggests medical distrust is as present in genomic medicine as it is in other medical fields. The disparity between the prevalence of medical distrust in white/European adults (35%) and Black/African American adults (43%) has been observed previously.[54] Our heterogenous sample allowed for some further disaggregation, showing Asian Pacific Islander adults prevalence of distrust at 39% and Hispanic/Latino adults with the lowest prevalence at 26%. Higher medical distrust was also seen in the transgender and non-binary/non-identifying gendered adults (64%), this confirms recent findings on medical mistrust in sexual minority populations.[62] With medical distrust identified as one of the largest barriers to participation in research[21,23,24], it may be safe to expect the higher levels of medical distrust in the general population.

Previous research predicting medical distrust found univariate associations between health care system distrust, gender, income, education, employment literacy and numeracy, but those relationships disappeared when multivariable models were used, leaving only depression status, coping skills, social engagement, and health literacy predicting distrust.[19,47] Other investigations of distrust have suggested that age, African American race/ethnicity, poorer health status, and lower income are reliably relate to health care system distrust [12,54]. The use of highest-quartile distrust scores may have increased our statistical power, thus our ability to identify predictors of distrust, over previous investigations.

Our findings show higher education and lower income were strong predictors of distrust in this sample. These associations have been captured previously in univariate analyses.[47] Higher education and lower income both predicting distrust stood out as odd, since these variables are typically positively correlated and association with them tend to move in the same direction. Marginal mean analysis of relationship between income and education offered some explanation, showing that adults with the highest education and lowest income had the highest probability of health care system distrust. We are unsure what part of a college education engenders medical distrust, but it may be more related to knowledge about limits of medical research or practice, or perhaps a greater knowledge medical history.

Difficulty accessing health care was another strong predictor of medical distrust and was selected in all three prediction models. Researchers have previously identified poor health care access as associated with medical distrust.[18,47,54] It is easy to conclude people who do not trust the medical system will not maintain a relationship with it. However, it may be that a system that provides health care, but does so with barriers too high to access, engenders distrust. While the current research does not provide direct evidence for one of these rationales over the other, it is important that both are given equal likelihood and the burden of distrust is not ascribed solely to the patient.

This research was undertaken with the hope of identifying patient characteristics associated with medical distrust in a population of adults willing to utilize medical genomic sequencing. This would allow us to target populations at risk for the negative effects of medical distrust with additional attentions from medical genetics providers, including several effective brief interventions designed specifically for the medical context, such as motivation interviewing. While this may still be a feasible option for addressing medical distrust, our pattern of results suggests there might be a deeper problem with the construct of medical distrust. Three of the six predictors of distrust in our final model directly identify populations that experienced historical victimization and ongoing stigmatization and marginalization within the medical context: Black/African American people, transgender, non-binary, and gender non-identifying people, and adults with serious mental illness. Higher prevalence of medical distrust in

African American adults has been observed reliability within the medical distrust literature.[12,47,54] Higher prevalence of medical distrust has also been identified in previous work examining transgender and non-binary/non-identifying populations and adults with poorer mental health status or serious mental illness.[47,62,63]

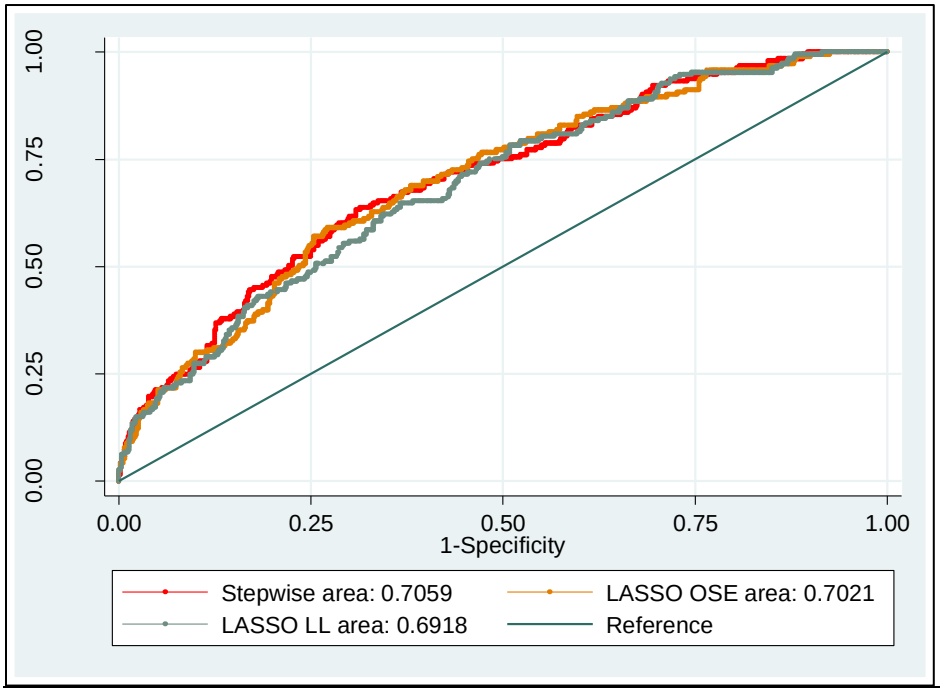
Armstrong, 2013, showed the strong positive association between African American racial/ethnic status and medical distrust reversed when experiences of medical and non-medical discrimination are adjusted for suggesting we need to overcome stigmatization inside and outside of the clinical setting.[64] Our work and others' suggest the experience of medical distrust may differ between marginalized and non-marginalized populations.[12] Specifically, medical distrust may be a proxy for exposure to historic and contemporary medical trauma and discrimination. In fact, there is a large degree of overlap between health behavior outcomes associated with medical distrust, and those associated with experiences of trauma. Notably, research examining the effect of trauma, both childhood and adult, has shown poorer adherence to treatment across multiple medical and behavioral health contexts including mental health care, HIV anti-retroviral treatment, and substance abuse treatment.[65-67] Additionally, childhood and adult trauma has also been associated with lower quality of life when compared to respective cohorts who have not experienced trauma.[68] We must confront the fact that a significant proportion of medical distrust is likely due to discrimination and stigma. Efforts to eliminate structural racism, discrimination, and other negative and stigmatizing power dynamics in the health care environment may be more successful at equitably improving health care outcomes than identifying and addressing medical distrust, including in genomic medicine. Trauma Informed Care may provide guidance for practice change necessary to address the needs of marginalized communities through its focus on avoiding re-traumatization and developing a clinical context that emphasizes provider trustworthiness, patient empowerment, and safety.[69,70]

This investigation utilized a sample of adults willing to receive genomic sequencing to understand the impact of medical mistrust on genomic medicine. This, combined with CHARM's focus on diversity in recruitment, lends our results a considerable degree of generalizability to heterogeneous

clinical settings similar to those medical genetics providers would encounter during practice. These findings should, however, be viewed considering a few limitations. Previous work that included distrust and experiences of medical and non-medical discrimination have been very productive.[54,62,64] Regrettably, these variables were not available for assessment in this body of evidence and would have added context to the current investigation. We hope this work provides a rational for future investigations of medical distrust to explore prediction variables beyond sociodemographic, health status and health care access. Finally, patterns of distrust in patients who volunteer for clinical genomic research may be different from those in the wider populations. This may be especially true of adults who will not agree to genomic screening or rarely enter the clinical setting. This work may not generalize to that population.

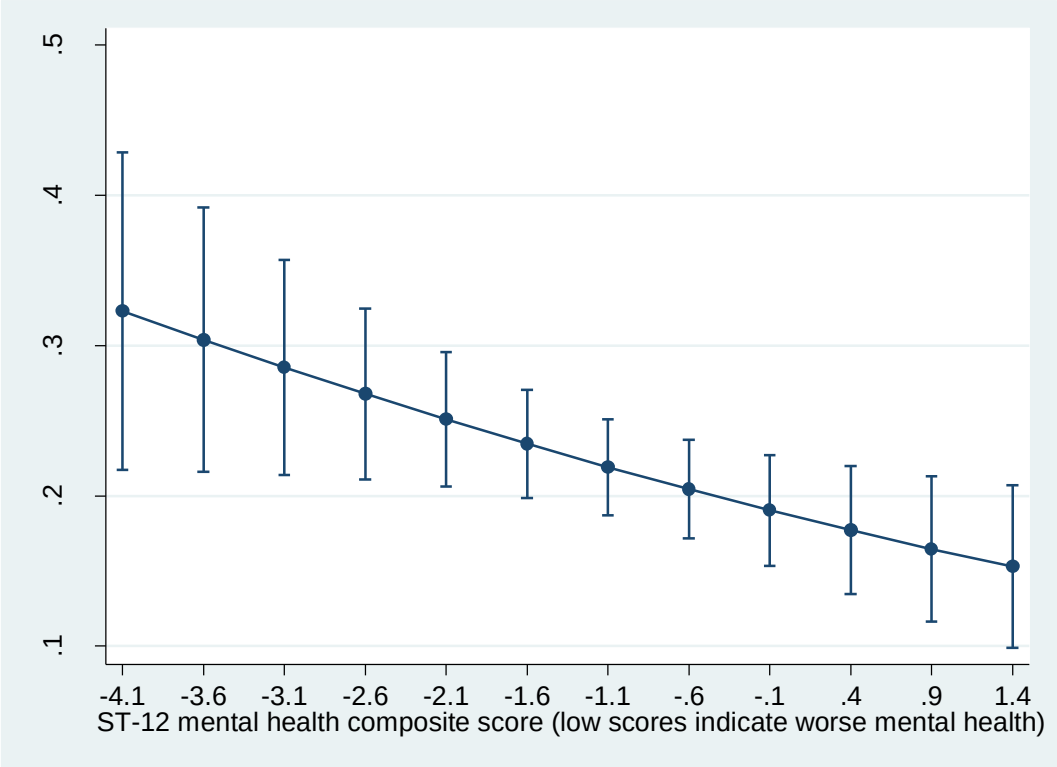
We found levels of medical distrust in the context of genomic medicine similar to that found in other medical research context.[47] The strongest prediction model of highest quartile medical distrust included higher education, lower income, poor health care access, African American racial/ethnicity status, transgender and non-binary/non-identifying gender identity, and poorer mental health. This work adds to the growing chorus of research questioning the definition and conceptualization of medical distrust. Future research would benefit from the inclusion of lived experiences of discrimination and how those impact provider interactions, health behavior, and health outcomes. Models of Trauma Informed Care may help health care providers build accommodations for participants who have experienced previous or ongoing stigmatization, abuse, or discrimination. This cannot be accomplished without efforts to elicit feedback from communities impacted by medical marginalization. It is incumbent on providers and medical systems to deliver these services with the goal of equitable outcomes for all patients.

Figure 2.1 Receiver Operator Characteristic Curves comparing Stepwise, LASSO OSE, and LASSO MSPE variable selection models



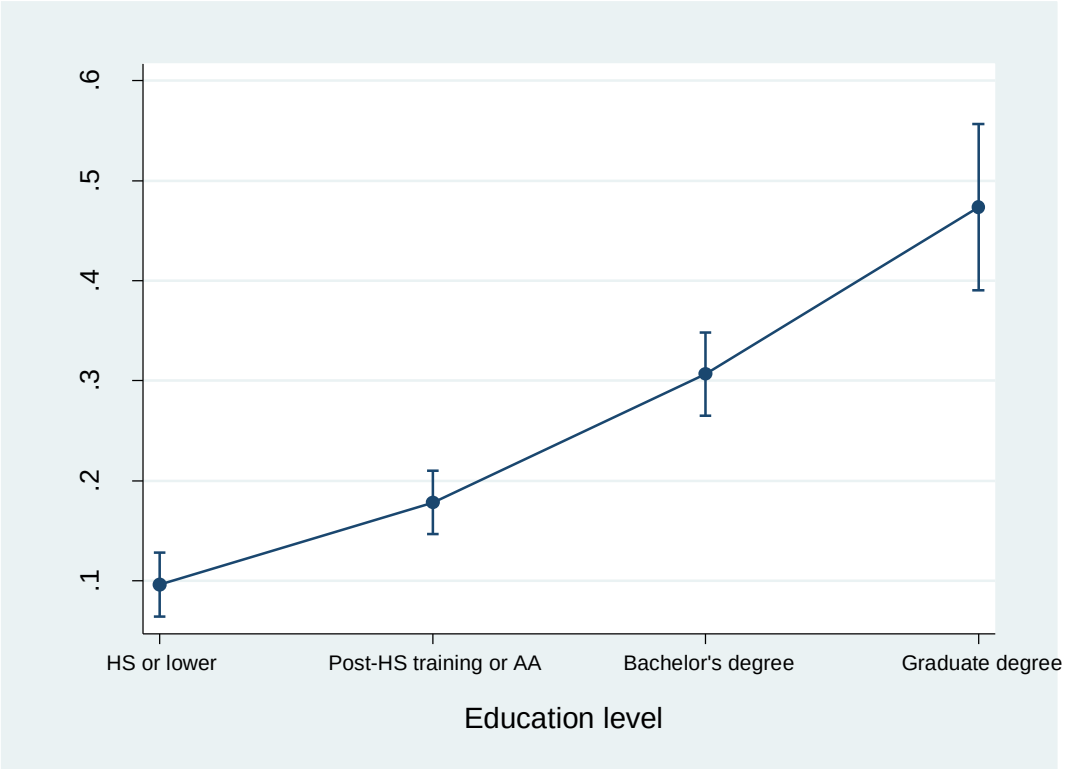
MSPE= largest lambda
OSE= one standard error

Figure 2.2: Probability of being in highest quartile HCSD score by SF-12 mental composite score



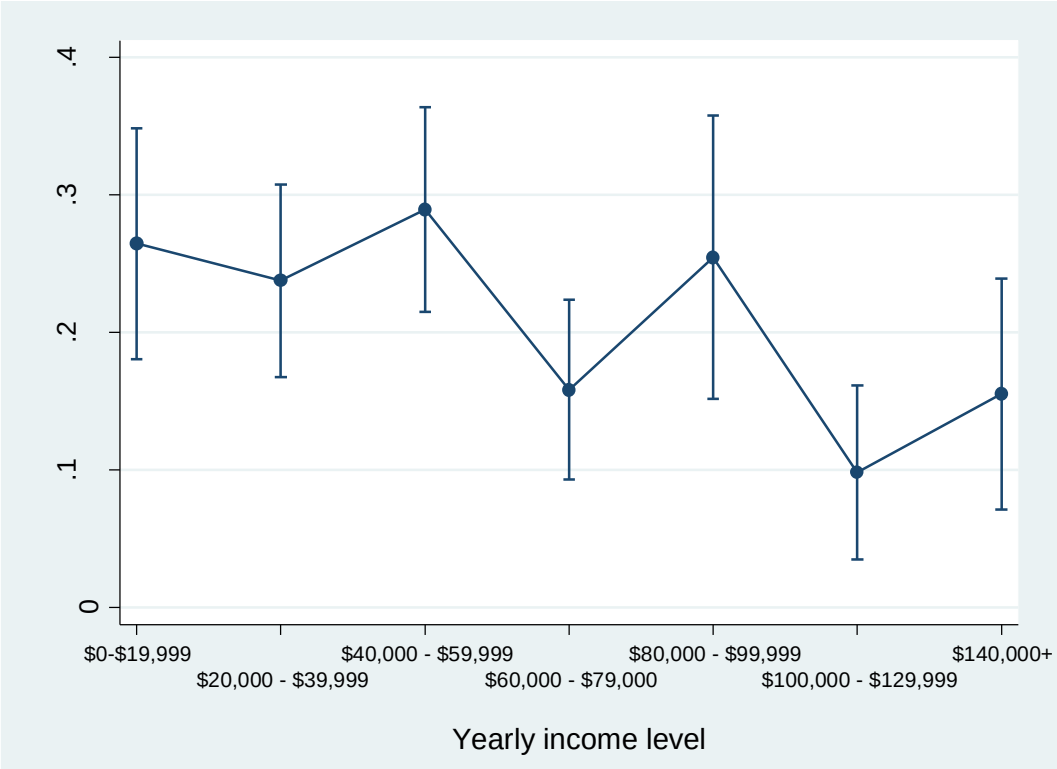
HCSD= Health care system distrust

Figure 2.3: Probability of highest quartile HCSD score by level of education



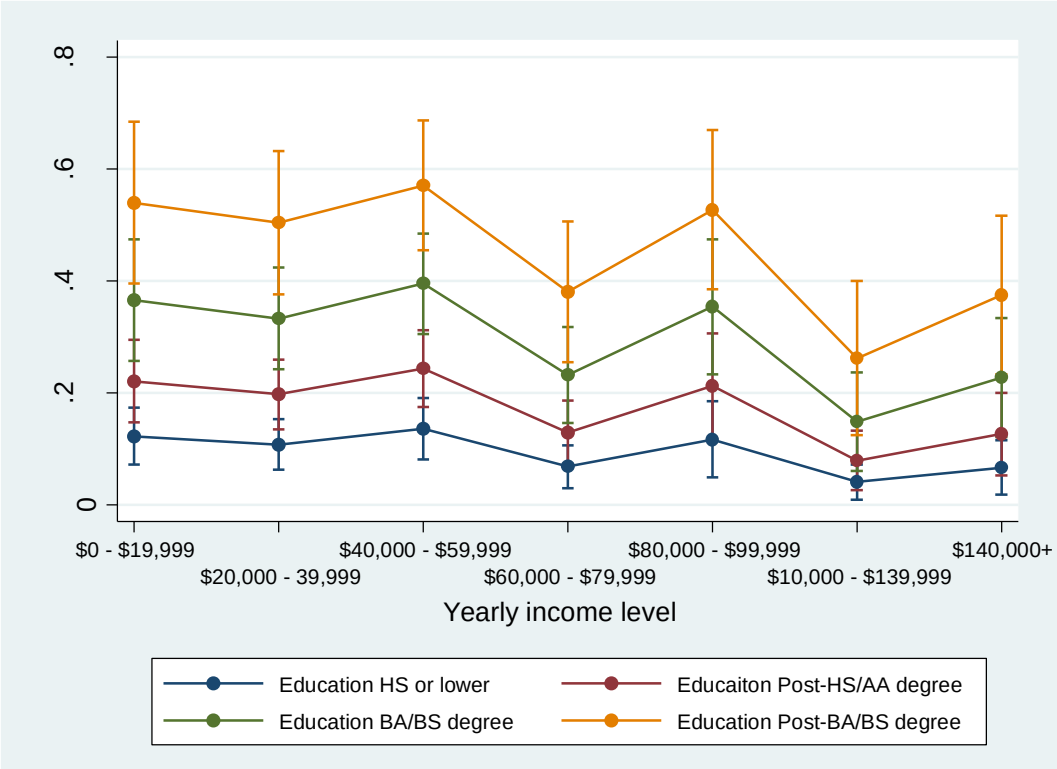
HS=high school
AA= Associates degree
HCSD= Health care system distrust

Figure 2.4: Probability of highest quartile HCSD score by income level



HCSD= Health care system distrust

Figure 2.5: Probability of highest quartile HCSD score by education level and yearly income



HCSD= Health care system distrust
HS=high school
AA=associate's degree
BA/BS= Bachelors of arts/ Bachelors of science

Table 2.1: Sample characteristics of total cohort				
	Study Cohort (N=824)			
	Mean (S.D.)	N	%	% in highest quartile distrust
Age	36.02 (8.24)			
Gender				
-Female		622	76	23
-Male		171	21	26
transgender and non-binary/non-identifying		22	3	56
Education				
High school graduate or less		186	23	11
Post-high school training or Associates degree		307	37	21
Bachelor's degree		198	24	34
Gradate or professional degree		132	16	38
Yearly Income				
$0- $19,999		142	17	23
$20,000 - $39,999		176	21	23
$40,000 - $59,999		167	20	32
$60,000 - $79,999		120	15	21
$80, 000 - $99,999		70	9	33
$100,000 - $119,999		77	9	13
$120,000 +		64	8	27
Race/Ethnicity				
Native American/ Alaska Native		51	6	22
Asian/ Pacific Islander		66	8	30
Black/ African American		67	8	34
White/European American		456	53	28
Middle Eastern/ North African		11	1	36
Hispanic/ Latino(a)		285	34	17
Multi-racial		100	12	35
Health Status				
SF-12 physical health composite	-0.02(1.12)			
SF-12 mental health composite	-0.97(1.22)			
HCSD score	25.21(6.13)			
Prevalence of high distrust (Gupta cut off)		266	32	

HCSD= Health Care System Distrust Scale

Table 2.2: Point prevalence of medical distrust by demographic sub-groups using Gupta, 2014 cut points

Race/Ethnicity	**N**	**Prevalence**
White/European	456	35%
All Minority	386	29%
Black/African American	67	43%
Asian Pacific Islander	66	39%
Hispanic/Latino	285	26%
Multi-Racial	100	42%
Gender		
Male	171	35%
Female	622	29%
transgender and non-binary/non-identifying	22	64%

Table 2.3: Multivariable logistic models comparing predictive variable selection of membership into highest HCSD quartile

Prediction model	**Backward Stepwise**	**OR(SE)**	**LASSO OSE**	**OR(SE)**	**LASSO MSPE**	**OR(SE)**
Variables	Race AA	1.70(0.49)*	Race AA	1.72(0.50)*	---	---
	---	---	Age years	0.98(0.01)	---	---
	Gender	1.45(0.24)*	Gender	1.41(0.23)*	Gender	1.42(0.23)*
	Education	1.56(0.10)*	Education	1.47(0.09)*	Education	1.47(0.09)*
	Income	0.86(0.05)*	---	---	---	---
	Low HC access	1.68(0.33)*	Low HC access	1.77(0.34)*	Low HC access	1.81(0.35)*
	SF-12 MHC	0.84(0.33)*	SF-12 MHC	0.82(0.06)*	SF-12 MHC	0.81(0.06)*
Mean pseudo R^2	0.108		0.096		0.088	
AIC/N	1.024		1.024		1.028	
BIC	838.49		845.83		840.65	

*= p<.10
HCSD -Health Care System Distrust Survey
OR -odds ratio
(SE) -standard error
--- -variable not selected in this model
LASSO -least absolute shrinkage and selection operator
LASSO OSE - LASSO method that chooses the largest λ value within one standard deviation of means squared predicted error.
LASSO MSPE - LASSO method that chooses least mean squared predicted error by using the largest available Lambda value.
Race AA - self-reported Black/African American race/ethnicity
HC-health care
SF-12 MHC-Short Form 12 mental health composite score
AIC/N -Akaike Information criterion divided by the number of people in the sample
BIC -Bayesian information criterion

Table 2.4: Final logistic multivariable model best predictive of highest quartile HCSD score, Pseudo-R^2=0.12

Variable	OR(SE)	Confidence interval
Race AA	1.77(0.52)	0.99 to 3.15
Gender		
Male	Referent	
Female	1.34(0.29)	0.88 to 2.05
transgender and non-binary/non-identifying	2.46(1.18)	0.95 to 6.34
Education		
High school or less	Referent	
AA or less	1.91(0.55)	1.08 to 3.37*
Bachelor's degree	5.45(1.66)	3.00 to 9.91***
Post-bachelor's degree	7.21(2.43)	3.71 to 13.99**
Income		
$0- $19,999	Referent	
$20,000 - $39,999	0.82(0.24)	0.46 to 1.47
$40,000 - $59,999	1.06(0.31)	0.60 to 1.87
$60,000 - $79,999	0.46(0.16)	0.24 to 0.90*
$80, 000 - $99,999	0.88(0.32)	0.43 to 1.79
$100,000 - $119,999	0.28(0.12)	0.12 to 0.64**
$120,000 +	0.51(0.21)	0.23 to 1.12
Low Access	1.74(0.35)	1.18 to 2.56**
SF-12 MH composite score	0.84(0.06)	0.72 to 0.98*

*=p<.05, **=p<.01, ***=p<.001
HCSD -Health Care System Distrust Survey
OR -odds ratio
(SE) -standard error
Race AA -self-reported Black/African American race/ethnicity
SF-12metnal health -Short Form 12 mental health composite score

Chapter 3. The Impact of Medical Distrust on personal utility perceptions of genomic screening and feelings associated with the receipt of genetic results

3.1 Abstract

Rational: Medical distrust is associated with many undesirable health behaviors including treatment non-adherence and is cited as the primary reason for non-participation in genetic research. Patient-level perceptions of, non-clinical, personal utility positively influence health behaviors related to the receipt of medical genetics care. Adults with positive feelings report better health outcomes and show better treatment decision making. The interplay of perceptions of personal utility and feelings about related genetic results, with regards to medical distrust, may help us craft messages that overcome treatment hesitancy and non-adherence related to medical distrust and encourage uptake of medical genetic screening.

Methods: Participants were recruited from Oregon state clinical settings within the Kaiser Permanente Northwest system and Denver Health, a system of federally qualified health centers in Colorado. Using patient-reported survey instruments, we measured the association between medical distrust, scored one to six, and 3 domains of non-clinical personal utility, scored one to seven, and medical distrust and feelings associated with receipt of genetic results, in a research sample of 843 adults. We assessed the relationships between measures using multivariable models, adjusting for known covariates of distrust.

Results: Our analysis suggests a significant relationship between medical distrust and perceived personal utility across three primary domains: anticipatory guidance (Beta=-.21; 95% confidence

interval:-.36 to -.05, p<.01), immediate benefit (B=-.20; 95% CI=-.32 to -.08, p<.01), and social benefit (B=-.23; 95% CI=-.36 to -.10, p<.01). No relationship was seen between medical distrust and feelings related to the receipt of genomic sequencing results.

Conclusions: We found medical mistrust may undermine patients' perceptions of personal utility of genomic sequencing. These results suggest that provider emphasis of immediate benefit of genomic sequencing, anticipatory guidance provided by genomic sequencing, and social benefits associated with sequencing may help overcome barriers to genetic medicine uptake attributable to medical distrust.

3.2 Introduction

Medical distrust has been identified as a strong driver of undesirable health behaviors including: lower rates of screening and treatment uptake, lower rates of treatment adherence, and poorer self-reported health and satisfaction with care in non-genetic related studies.[14,15,44,71,72] Higher prevalence of medical distrust is often reported in some populations of adults who identify as racially/ethnically diverse.[21-24,72] Unfortunately, there is a dearth of information about the impact of distrust in the context of clinical genomic sequencing. If the impacts of medical distrust on clinical genomic medicine are similar to the impacts of distrust in other medical contexts, it may result in lower screening, and adherence, thus delaying equitable care. The higher prevalence of medical distrust in racially/ethnically diverse populations may directly blunt the positive impact of genetic medicine and disproportionality impact historically underserved populations.

Evidence suggests patient-level characteristics are pivotal in the decision to adopt new medical technologies, and receipt of and adherence to medical care.[27,73,74] Little or no work on

the impact of medical distrust on genomic sequencing has been conducted in populations of adults wiling to receive clinical genomic sequencing. This limits the ability to draw conclusions about the effect of medical distrust on treatment recommendations stemming from medical genetic sequencing results. Examining how the complex collection of patient-level characteristics interacts in populations willing to utilize new technologies, such as genomic sequencing, may help inform our efforts to overcome barriers to receipt of genetic medicine.

A unique benefit of genetic medicine is the ability to use results for future planning, beyond immediate clinical utility[75] including family planning, financial planning, or putting in place advanced directives. Researchers investigating these perceptions have termed the construct 'personal utility'. Recent research suggests that high medical trust is associated with higher personal utility beliefs regarding medical genetic sequencing.[76] Further work suggests an association between personal utility perceptions and uptake of medical genetic sequencing technology.[75] Given that medical distrust has a negative impact on genetic screening and other related health behaviors, investigating the relationship between personal utility perceptions and medical distrust may provide insights into patients' decision making processes during uptake of medical genetic sequencing.

Moreover, feelings associated with genetic screening results are a topic of concern for patients' mental health after receiving potentially life-altering information about future health risks.[77-81] Researchers have observed links between negative emotions, decisional conflict, and later risk management decision making after positive genetic cancer screening.[82] In chronic disease settings negative mood has been associated with reduced treatment adherence.[83,84] The association between negative mood, decisional conflict and treatment adherence may hold true in genomic sequencing for disease as well. Close and trusting patient-provider relationships may

mitigate the negative impact and influence acceptance of genetic results and positive psychological adaptation.[85] Understanding the influence of medical distrust on feelings associated with medical genetic sequencing results could help focus support for patients who may be at risk for decisional conflict or may have difficulty making risk management decisions.

The goal of the current research is to examine the impact of medical distrust on constructs distinct to clinical genomic sequencing, specifically, personal utility of genetic testing, and feeling related to receipt of genetic results. Understanding the interplay of these patient-level factors may help us improve acceptance and uptake of clinical genomic screening and health behavior recommendations that stem from medical genetic sequencing.

3.3 Methods

3.3.1 *Conceptual model*

The conceptual framework for this research is adapted from one presented in Armstrong et al., 2016 (Figure 1.1). Patient-level characteristics influence cognitive bias, in this case medical distrust, that are brought into the clinical encounter. After the encounter, the existing bias along with perceptions and emotions surrounding the encounter undergo an affective-cognitive appraisal evaluating information received from clinicians about a patient's health and health behavior. The result of these evaluation influence patient decision making about health behavior change and ultimately influences health outcomes.

3.3.2 *Data source*

This work was conducted as part of a larger study investigating the implementation, clinical utility of exome sequencing for heritable cancer risk in a divers sample of adults , Cancer Health Assessment Reaching Many (CHARM) .[48,49] Eligibility criteria included screening at

high-risk either on the Probe Empower Manifest Lynch syndrome screening tool[50], or moderate to high-risk on the Brest Cancer Genetics Referral Screening Tool[51], or having an unknown family histories of cancer and Lynch syndrome. Participants received whole exome sequencing to screen for Lynch Syndrome and heritable breast and ovarian cancer risk as part of study protocol. Further information about the CHARM protocol and methods can be found elsewhere.[48] Research staff enrolled 842 adults, aged 18-49 years, during the two-year recruitment period, with an overarching goal of high racial/ethnic diversity amongst their adult population. The CHARM study target recruitment at clinics who provided care to highly diverse populations, specifically the Rockwood, North Lancaster and Gateway clinics within the Kaiser Permanente Northwest system, and 3 clinics from the Denver Health system, a Federally Qualified Health Center. When possible, study staff recruited in the clinics in-person, although many were recruited through postal and electronic messaging.

Consented participants completed survey measures, including demographic information and a medical distrust assessment, and provided a biological sample for sequencing at their baseline time point. They were then randomized to either regular genetic counseling or low-literacy counseling. Approximately 8 weeks later, participants were contacted with their results and provided genetic counseling if they had positive results for heritable cancer risk. After receiving results, participants completed surveys including questions about their perceptions of the non-clinical utility of genomic results and feelings about their genomic results. A third and final time point followed with additional survey materials 8-weeks later. Only data from the first two time points were used for the current analyses.

.3.4 *Predictor Variable*

The health care system distrust scale (HCSD) assesses medical distrust in health care organizations including clinics, hospitals, insurance organizations, and testing laboratories.[52] We chose the HCSD based on its status as one of the "gold standard" measures of medical distrust and its broad history in the literature.[26] The HCSD is a 9-item scale Likert scored 1 to 5 from strongly disagree to strongly agree. Scoring instructions generate a total score between 9 and 45 with higher scores indicating greater levels of distrust. For ease of interpretability, we collapsed the HCSD scores to 1-6 with higher scores, again, related to greater medical distrust. The HCSD has been previously psychometrically validated and is considered one of the gold-stand measures of medical distrust.[19,26,43,52,54,64,86]

3.3.5 *Outcome variables*

The first outcome of interest was the perception of personal utility of genetic testing. We chose the Patient Reported Utility Scale (PRU) to measure personal utility because it inquiries specifically about genetic medicine utility perceptions.[87] Items for the PRU were generated systematically using a Delphi method, and the measure is currently undergoing full psychometric validation.[87] The PRU is made up of 17 items categorized into three primary domains: anticipatory guidance, immediate benefit, and social benefit. Within the three primary domains, there are 9 subdomains: ability for future planning, reproductive autonomy, mental preparation, self-knowledge, enhancing coping, value of information, changes to social support, communication with relatives, and feeling good helping others. The PRU is scored on a 1 to 7 Likert scale from strongly disagree to strongly agree. For the current analyses, items linked to specific domains and subdomains were summed then divided by the number of items with the

domain or subdomain, generating a, 1 to 7, mean domain/subdomain score with higher scores indicating greater personal utility.

The second outcome of interest was self-reported feelings associated with receipt of genetic results measured using the Feelings About Genomic Testing Results (FACToR) scale.[88] The FACToR is based on the Multidimensional Impact of Cancer Risk Assessment (MICRA).[77] It expands the scope of the MICRA beyond cancer screening to all genetic sequencing results. While not yet widely utilized, the FACToR has undergone full psychometric validation. There are four domains within the FACToR: positive feelings, negative feelings, uncertainty about results, and privacy concerns. The 12-items of the FACToR are scored on a 0 to 4 Likert scale, from "Not at all" to "A great deal". When summed, the positive feelings subscale generates a 0-16 score, the Negative feelings (reversed) subscale generates a 0-12 score, the uncertainty subscale generates a 0-12 score, and the Privacy concerns subscale generates a 0-8 score with higher scores associated with greater levels of feeling.

3.3.6 *Statical analyses*

We used the collapsed HCSD total score for the predictor variable of interest for each multivariable model. All models included identical adjustment variables and predictor variable of interest (HCSD collapsed score). Adjustment variables were minority status, gender identity, age education, income, type of genetic results, and type of genetic counseling received. Robust standard errors were chosen to lower the impact of possible outliers. Only data from participants with complete case data were included in these analyses.

Our analyses necessitated the use of three domain specific models for the PRU and 9 sub-domain specific models. The number of items per domain/sub-domain are listed in table 2. and table 3, respectively. We treated mean domain/sub-domain scores from the PRU models as

continuous variables and employed linear regression models. We adjusted for multiple comparisons using the Bonferroni corrections.

The analyses examining the FACToR sub-scales consisted of 4 individual models, one for each sub-scale. The outcome variables for these models, FACToR subscale scores, were summed as recommended in the validation literature and treated as continuous variables.[88]

We chose adjustment variables based on known covariates of medical distrust found in the literature. Adjustment variables consisted of: Racial/Ethnic minority status coded dichotomously (1 = minority, 0 = non-minority) , gender coded nominally (Male, female, non-CIS gender identity), age coded ordinally, 1 to 3 (18 to 29 years, 30 to 39 years, and 40 or above), Education coded ordinally, 1 to 3 (high school degree or less, some college to college degree, and post-college education) Income coded ordinally, 1 to 3 ($39,999 or less, $40,000 to $79,999, and $80,000 or above), type of genetic result coded nominally (negative, uncertain, positive) and type of genetics counseling received coded nominally (1 = literacy focused, 0 = treatment as usual). An interaction between type of genetic result and distrust was be included in all models to test possible moderation effects that could interfere with results interpretation.

3.4 Results

The complete case sample of 574 participants was predominantly female (77%) with a mean age of 36 years (Table 3.1). Racial/ethnic minorities adults were well represented in this sample (42%). Many participants (45%) had either a college degree or some post-baccalaureate education and the largest proportion of this sample made $39,999 or less in the previous year (36%).

The PRU domain-specific results suggest that as health care system distrust increases, the perceived utility of genetic screening decreases significantly across all three domains (Table 3.2). There is a significant negative association between health care system distrust and the following sub-domain scores: ability for future planning, mental preparation, self-knowledge, enhanced coping, communication with relatives, and helping others (Table 3.3). There was no significant association between the HCSD score and the sub-domain scores for reproductive autonomy, value of information, and change social support. The results of the interaction between HCSD and type of genetic results were again non-significant and can be seen with the coefficients of the adjustment variables (Table 3.4).

The results of the final four models using the FACToR subscales: positive feelings, negative feelings, uncertainty, and privacy concerns are presented in table 4. Scores generated using the HCSD were not significantly related to FACToR subscales after controlling for adjustment variables. No interaction between HCSD score and results type were observed.

3.5 Discussion

Our analyses found a significant negative relationship between medical distrust and all three of the domains and most of the sub-domains of the PRU. We did not identify a relationship between medical distrust and any of the FACToR subscales: positive, negative, uncertain, or privacy concerns.

All domains of perceived utility were significantly negatively related to medical distrust as well as most personal utility sub-domains, suggesting a robust relationship between distrust and perceptions of personal utility. These associations may offer clues about how medical distrust impacts health behavior by undermining perceptions of care usefulness. While further

work investigating this relationship should be completed, it may be possible that emphasizing personal non-clinical utility perceptions of genetic medicine may positively influence screening and overcome treatment hesitancy attributable to medical distrust. The clear topics explored by the domains and sub-domains of the PRU may provide important subject matter for genetics-providers and genetics-counselors to address during patient interactions with patients who cite medical distrust.

Our work suggests that this personal utility influences other related constructs similarly to what you would expect in a model of health behavior.[27,73] Specifically, personal utility is negatively associated with medical distrust, and this relationship is influenced by other patient-level barriers including age, and minority status. This suggests personal utility is an important construct when modeling medical distrust in genomic medicine and provides evidence of convergent validity for the construct.

We are unsure why some sub-domains of personal utility were significantly related to medical distrust, and other were not. Since the psychometric validation of the PRU is being conducted concurrently with this research, there is the possibility that these sub-domains may change or be eliminated in future versions of the instrument.

With negative feelings being a hallmark of depression, and previous findings showing an association between distrust and depression, we were surprised to find no relationship between distrust and negative feelings associated with results of genetic information. Lack of this finding may suggest that other components of depression may contribute to distrust; negative feelings alone did not explain the relationship. Interestingly, despite overlap between undesirable health behaviors associated with medical distrust and undesirable health behaviors associated with

negative feelings, the effects of medical distrust and negative feelings from genetic results may operate independently but cause similar outcomes.

The body of academic literature that evaluates associations between medical distrust and adoption of genetic medicine is severely limited; and most of it utilized focus groups of patients who may or may not have received medical sequencing.[21-23] Utilizing a research sample of adults who underwent clinical genomic sequencing, as this investigation did, allows us to generalize our results to patient populations whom are likely to interact with their providers in clinical settings. The generalizability of this work is further enhanced by the ability of the parent research study to recruit a very racially and ethnically diverse sample. With that in mind, it should be stated that this research sample is self-selecting, and may findings not be generalizable to populations who are medically hesitant or resistant to research participation.

Future research should continue efforts to identify psycho-social variables that impact uptake and interaction with genomic medicine. Further exploration should include additional variables assessing perceptions of clinical utility and patient experiences with medical genetic care. Understanding these relationships can inform areas where patient education and the provision of information can be most effective to aid in screening uptake and treatment adherence.

Table 3.1 Sample characteristics		
	Study Cohort (N=574) Mean (S.D.)	
HCSD score	25.19(6.08)	
Age	36.37 (8.64)	
Gender	**N**	**%**
Female	442	77.00
Male	123	21.42
transgender and non-binary/non-identifying	9	1.58
Education		
High school graduate or less	119	34.66
Post-high school training or certificate but no bachelor's degree	198	34.45
Bachelor's degree or graduate professional degree	257	44.76
Yearly Income		
$0- $39,999	207	38.67
$40,000 - $79,999	198	35.34
$80, 000 +	169	25.97
Race/Ethnicity		
White or European American	328	57.15
Racial/Ethnic minority	246	42.85

HCSD= Health Care System Distrust Scale

Table 3.2: Impact of health care system distrust on utility belief categories

Domain (items per domain)	N	Coefficient (S.E.)	95% C.I.
Anticipatory guidance (5)	557	-0.20 (0.08)	-0.36 to -0.08**
Immediate benefit (7)	554	-0.20 (0.06)	-0.32 to -0.08**
Social benefit (5)	555	-0.23 (0.07)	-0.36 to -0.10**

**=p<.01
S.E. -Standard Error
95% C.I. -95% confidence interval
Bonferroni correction applied across series of tests
Adjustments included in model: age, gender, race/ethnicity, income, education, genetics result, and type of counseling received

Table 3.3.: Impact of health care system distrust on utility belief sub-domains

Sub-domain (number of items)	N	Coefficient (S.E.)	95% C.I.
Ability for future planning (2)	562	-0.21 (0.09)	-0.38 to -0.05**
Reproductive autonomy (2)	558	-0.18 (0.10)	-0.37 to 0.02
Mental preparation (1)	563	-0.24 (0.09)	-0.41 to -0.07**
Self-knowledge (2)	560	-0.23 (0.08)	-0.36 to -0.11**
To enhance coping (3)	558	-0.22 (0.08)	-0.37 to -0.07**
Value of information (2)	561	-0.09 (0.06)	-0.21 to 0.02
Change social support (1)	562	-0.22 (0.10)	-0.42 to -0.02
Communication with relatives (1)	562	-0.26 (0.09)	-0.44 to -0.08**
Feeling good helping others (3)	555	-0.23 (0.06)	-0.35 to -0.11**

**=p<.01
S.E. -Standard Error
95% C.I. -95% confidence interval
Bonferroni correction applied across series of tests
Adjustments included in model: age, gender, race/ethnicity, income, education, genetics result, and type of counseling received

Table 3.4: Impact of healthcare system distrust on Feelings about genetic results

Domain	N	**Coefficient (S.E.)**	**95% C.I.**
Positive feelings	558	-0.29 (0.31)	-0.91 to 0.33
Negative feelings	565	-0.01 (0.07)	-0.14 to 0.16
Uncertainty	559	-0.01 (0.08)	-0.15 to 0.17
Privacy concerns	560	-0.06 (0.08)	-0.21 to 0.09

***=p<.001, **=p<.01, *=p<.05
S.E. -Standard Error
95% C.I. -95% confidence interval
Bonferroni correction applied across series of tests
Adjustments included in model: age, gender, race/ethnicity, income, education, genetics result, and type of counseling received

Table 3.5 Adjustment coefficient by Utility Domain						
Adjustment Variable	**Anticipatory Guidance**		**Immediate Benefit**		**Social Benefit**	
	Coeff. (S.E.)	**95% C.I.**	**Coeff. (S.E.)**	**95 % C.I.**	**Coeff. (S.E.)**	**95% C.I.**
Age yr.						
18-29	Referent					
30-39	0.05(0.18)	-0.29 to 0.40	-0.06(0.14)	-0.22 to 0.33	0.14(0.15)	-0.15 to 0.42
40+	-0.37(0.18)	-0.74 to -0.01*	-0.02(0.16)	-0.33 to 0.29	0.19(0.16)	-0.13 to 0.49
Income						
<$39,999	referent					
$40,000- $79,999	0.08(0.17)	-0.24 to 0.40	0.04(0.13)	-0.22 to 0.29	0.16(0.14)	-0.11 to 0.42
$80,000+	-0.06(0.19)	-0.44 to 0.31	0.19(0.15)	-0.10 to 0.48	0.04(0.16)	-0.26 to 0.34
Gender						
male	Referent					
Female	-0.25(0.16)	-0.57 to 0.07	-0.11(0.12)	-0.36 to 0.13	-0.30(0.14)*	-0.57 to -0.03
non-cis	0.15(0.21)	-0.26 to 0.57	0.36(0.25)	-0.07 to 0.94	-0.18(0.31)	-0.80 to 0.42
G.C. type						
TAU	referent					
letter	-0.58 (0.24)	-1.06 to -0.11*	-0.45(0.19)	-0.84 to -0.07*	-0.48(0.20)	-0.86 to -0.10*
Modified	0.88 (0.14)	-0.39 to 1.06	0.16(0.10)	-0.05 to 0.37	-0.24(0.75)	-0.25 to 0.20
Racial/Ethnic Minority status						
Non-minority	Referent category					
Minority	0.12 (0.60)	0.18 to 0.76*	0.36(0.12)	0.14 to 0.59*	0.33(0.12)	0.08 to 0.57*
Education						
HS or less	Referent					
College or less	0.14(0.19)	-0.24 to 0.51	0.34(0.16)	0.03- 0.65*	0.12(0.16)	-0.20 to 0.44
Post-grad	-0.12(0.20)	-0.57 to 0.56	0.18(0.17)	-0.14- 0.51	-0.27(0.17)	-0.60 to 0.07
Genetic Results Category						
Negative	Referent category					
Uncertain	-0.05 (0.88)	-1.79 to 1.69	0.51 (0.58)	-0.62 to 1.65	0.21 (0.56)	-0.88 to 1.31
Pathogenic	0.024 (0.49)	-0.72 to 1.20	-0.18 (0.38)	-0.92 to 0.56	-0.04 (0.39)	-0.73 to 0.81
Interaction coefficient by PRU Domain						
Adjustment Variable	**Anticipatory Guidance**		**Immediate Benefit**		**Social Benefit**	
	Coeff. (S.E.)	**95% C.I.**	**Coeff. (S.E.)**	**95 % C.I.**	**Coeff. (S.E.)**	**95% C.I.**
HCSD*genetic results type (negative, uncertain, positive)						
Negative	Referent category					
Uncertain	-0.06 (0.26)	-0.56 to 0.44	-0.24 (0.17)	-0.63 to 1.70	0.05(0.11)	-0.17 to 0.27
Pathogenic	-0.09 (0.14)	-0.37 to 0.19	0.03 (0.11)	-0.19 to 0.24	-0.01 (0.38)	-0.23 to 0.22

*=p<.05
S.E. -Standard Error
95% C.I. -95% confidence interval
TAU – Treatment as usual
HS – High school
Non-cis – self-reported non-cis gender identity
Post Grad – post college graduate education

Chapter 4. The Impact of Medical Distrust on Health Behavior and Results Sharing in a Medical Genomic Research Context

4.1 Abstract

Rational: Medical distrust can negatively impact a wide range of health behaviors, including lower rates of cancer screenings, vaccination uptake, and treatment adherence. Medical distrust is also cited as the primary reason for unwillingness to participate in genomic research. However, little work has been done to explore the impact of medical distrust on health behaviors and willingness to discuss results with health care providers and family in the medical genomics context.

Methods: We assessed medical distrust in a research sample of adults (N=433) receiving genomic sequencing to screen for heredity risk of cancer syndromes. Participants were recruited from clinics in two different health systems, the Kaiser Permanente Northwest vertically integrated health care system, and Denver Health, an integrated safety-net health system of federally qualified health care centers in Colorado. We utilized multivariable logistic regression to evaluate the association between medical distrust and patient-initiated health behavior change or intent to change and genomic results sharing or intent to share. Observed associations were checked for mediation effects by perceptions of personal utility of genomics.

Results: Medical distrust was not significantly associated with change or intent to change patient-initiated health behaviors or change or intent to discuss genomic results with provider. Medical distrust had a negative association with sharing or intent to share results among family

members (odds ratio 0.72, confidence interval: 0.54 to 0.97). Exploratory mediation analyses revealed a significant influence of personal utility perceptions, anticipatory guidance, immediate benefit, and social benefit, on the relationship between medical distrust and sharing or intent to share genomic results with family members.

Conclusions: Medical distrust may pose a barrier to family genomic results sharing but is not associated with discussion of results with provider or patient-initiated health behavior change. Mediation suggests personal utility is a mechanism by which medical distrust impacts family genomic results sharing that could be targeted by intervention. Further exploration of additional mediators of distrust and undesirable health behaviors may allow us greater insight into how to address the negative impacts of medial distrust.

4.2 Introduction

An established body of evidence has demonstrates that medical distrust, the belief that the medical system may act against patients' best interests, is a consistent barrier to health care.[19,43,89,90] Researchers have observed that medical distrust is associated lower cancer screening rates, poorer medication adherence, and lower health information disclosure with doctors.[14,15,25,44,91] There is a dearth of research investigating the impact of medical distrust in the context of medical genomics, with existing work focusing primarily on distrust as a barrier to research participation and its effect on genomic sequencing uptake .[22-24,29]

Medical genomic sequencing identifies heritable disease risk. To realize the benefit of medical genomics, patients must discuss genomic results with knowledgeable providers and receive and follow medical recommendations regarding treatment decisions and preventative health behavior changes such as early clinical interventions, adapted disease screening schedules

or lifestyle changes.[92] If medical distrust in the context of genomic sequencing is analogous to its impact in other medical fields, distrust may directly undermine many of the benefits patients receive from sequencing through lower screening rates, poorer treatment adherence, or lower rates of medical information disclosure with their provider.[15,18,44,54] The limited scope of current research prevents investigators from drawing firm conclusions about the effects of medical distrust on health behavior changes after receiving medical genomic sequencing results and willingness to discuss genomic sequencing results with health care providers.

Clinical genomic sequencing has a unique additional benefit; genomic results about heritable disease risk can be shared among family members allowing family-wide health benefits.[93] These results represent a valuable tool to inform family members about the risks of heritable disease and the importance of screening or other forms of medical engagement. This added benefit maybe lost if medical distrust limits or prevents genomic results sharing among family members.[94] Familial sharing of health information, and recommendations for screening or treatment are particularly influential among Latinx and African American families.[38-42] Any impact of medical distrust that limits familial sharing may disproportionately impact these populations.

Examining the impact of medical distrust on genomic results sharing and health behavior change allows us to estimate the threat medical distrust poses to the benefits of medical genomic sequencing. The intent of the current investigation was to assess patient-initiated health behavior changes after receipt of sequencing results and examine the extent to which medical distrust is a barrier to genomic results discussion of results with health care providers and genomic results sharing with family members. Based on associations between distrust and perceptions of the personal utility of genetic results found in previous research[95], we also investigated whether

personal utility beliefs could partially explain the impact of medical distrust on health behaviors and health information sharing through mediation analysis.

4.3 Methods

4.3.1 *Conceptual model*

To guide this research we adapted a conceptual framework of the impact of medical distrust on health outcomes (figure 1.1).[19] This model asserts that patient-level characteristics influence they type of cognitive biases patients bring into a clinical encounter (medical distrust in the current analyses). After the encounter, these biases along with feelings and perceptions about the encounter, are used to appraise medical information, and provider recommended health behavior changes. The results of the cognitive-affective appraisal determines whether health behavior will change, and ultimately influence health outcomes.

4.3.2 *Data sources*

These analyses were completed as part of a larger parent-study, Cancer Health Assessment Reaching Many (CHARM).[48] Enrollment criteria required a result of "high-risk" after screening with the Probe Empower Manifest Lynch syndrome screening tool[50], or a moderate to high-risk result on the Brest Cancer Genetics Referral Screening Tool[51]. Participants with an unknown family history of heritable cancer and Lynch syndrome were also included. As part of the study participants received whole exome sequencing for Lynch Syndrome and heritable breast and ovarian cancer risk. During the two-years recruitment period study staff consented 842 adults, aged 18-50 years. CHARM researchers targeted clinics providing care for highly racially/ethnic diverse populations. These sites included the Rockwood, North Lancaster and Gateway clinics within the Kaiser Permanente Northwest system, the East Denver and Aurora clinics within the Kaiser Permanente Colorado system, and three sites in the Denver

Health system which were all Federally Qualified Health Centers. Study staff recruited participants in-person from the clinics, when possible, although some participants were recruited through postal and electronic messaging.

CHARM participants completed a battery of survey measures, including demographic information and medical distrust assessment, and provided a biological sample for genomic sequencing at baseline. At 8-weeks study staff contacted participants with their results and randomized them to one of two types of genetics counseling. Participants also completed a second battery of surveys items including perceptions of the personal utility of genetic results. At 16-weeks participants completed a final survey battery which included novel questions about patient-initiated health behavior changes and sharing or intent to share genomic results with health care providers and family members. Our analyses utilized medical distrust, assessed at baseline, perceptions of utility and feelings about genetic results collected at week-8, and intent to change health behavior and intent to discuss and share genomic results collected at week-16.

4.3.3 *Predictor variable*

The primary construct of interest was medical distrust, which we measured using the Revised Health Care System Distrust Scale (HCSD).[52] The HCSD is considered to be one of the gold standard measures of medical distrust having been utilized in multiple investigations of medical mistrust.[26] The current HCSD has been revised 3- times and is psychometrically validated.[19,26,43,52,54,64,86] The 9-itmes of the HCSD are scored on a 1 to 5 Likert scale (strongly agree to strongly disagree) generating a final score between 9 and 45 with higher scores indicating greater medical distrust.[52] For these analyses the predictor of interest was HCSD total score (9 to 45) collapsed to 1 to 6, for ease of interpretation.

4.3.4 *Outcome variables*

Patient-initiated health behavior changes were measured by asking participants "Have you made any changes in your health care or lifestyle, not based on medical recommendations made by your doctor or health care provider?" For this question participants were allowed to answer "yes", coded 1 or "no", coded 0. Discussion of genomic results with provider was measured using two questions. Participants were asked "Did you discuss your genetic test results with your/your child's doctors or health care providers?" and provided answers "yes, not yet but I plan to, or no and I don't plan to". For the purposes of the current analyses the answers "yes", and "no, but I plan to" to were combined and coded 1= shared or intent to share, and 0=did not share and does not intend to. Participants were then asked, "Since receiving your/your child's study results, have you shared the information with any biological family members (blood relatives)?". Participants were provided with options to answer this question "yes, I haven't shared this information yet, but plan to in the future, and I didn't share this information with anyone". The answers "yes" and "I haven't shared this information yet, but plan" to were combined and coded 1; the answers "I didn't share this information with anyone" were coded 0.

4.3.5 *Adjustment variables*

We chose adjustment variables based on previously found associations with medical distrust. Our current series of analyses included racial/ethnic minority status, gender, age, education, income. Type of genomic results was added because of the association between genomic results and health behavior change.[96] An interaction between type of genomic result and distrust was included to account for differential effects of distrust on outcomes in individuals receiving negative, positive, or inconclusive results .[96] Type of genetic counseling received was adjusted as a design variable.

The adjustment variables were coded as follows: racial/ethnic minority status coded dichotomously (1 = minority, 0 = non-minority) , gender coded nominally (Male, female, non-CIS gender identity), age coded ordinally, 1 to 3 (18 to 29 years, 30 to 39 years, and 40 or above), Education coded ordinally, 1 to 3 (high school degree or less, some college to college degree, and post-college education) Income coded ordinally, 1 to 3 ($39,999 or less, $40,000 to $79,999, and $80,000 or above), type of genomic result coded nominally (negative, uncertain, positive) and type of genetics counseling received coded nominally (1 = literacy focused, 0 = treatment as usual). An interaction between type of genomic result and distrust was included in each model to test possible moderation effects that may interfere with results interpretation.

4.3.6 *Mediation variables*

The Patient Reported Utility Scale (PRU) inquiries specifically about genetic medicine utility perceptions.[87] Items for the PRU were generated systematically using a Delphi method, and the measure is currently undergoing full psychometric validation.[87] The PRU is made up of 17 items categorized into three primary domains: anticipatory guidance, immediate benefit, and social benefit. The PRU is scored on a 1 to 7 Likert scale from strongly disagree to strongly agree. For the mediation analyses, items linked to specific domains were summed then divided by the number of items within the domain or subdomain, generating a one-to-seven mean domain score with higher scores indicating greater personal utility perceptions.

4.3.7 *Statistical analyses*

We used three multivariable logistic models to examine the effects of medical distrust on health behavior outcomes of interest: patient-initiated health behavior change, discussing or intent to discuss genomic results with health care provider, and sharing or intent to share

genomic results with family. Each of these individual models included identical adjustment variables.

To explore possible mediation by personal utility belief domains, we used product of coefficients approach, as described by Baron and Kenny, with standardized coefficients and the above listed control variables.[97,98] This method uses a combination of linear and logistic regression to estimate direct(c'), indirect (ab), and total effects (c) in the mediation relationship (figure 4.1). The statistical significance of the standard error of the direct and indirect pathways were tested using bias-corrected bootstrap confidence intervals (1000 replications).[99,100] Stata 14 software and the binary_mediation package was used to conduct all statistical analyses[101,102]

4.4 Results

Of the original 843 participants consented, only 430 were included in our complete case analyses due to missing data from the week-16 time point. Sociodemographic characteristics of the study sample, and the sample lost to follow up can be seen in Table 2. A series of t-tests and chi^2 tests were performed comparing the demographic data on the complete case sample to the sample of participants lost to follow up. Racial/ethnic minority status (x^2 (1 N=780)=22.91, p<.05) and lower education (x^2 (3 N=843)=14.67, p<.05) were associated with missing data at the week-16 time point. The complete case sample was predominantly female (76%), with a mean age of 36 years (S.D.=8.5). Racial ethnic minority adults were well represented in this sample (46%). Forty percent of the sample had earned a college degree or had completed some post-baccalaureate education. The largest proportion had an income of $40,000 per year or less.

The results of the multivariable logistic regression analyses are shown in Table 3. HCSD score was not associated with patient-initiated health behavior change (OR=1.04, CI: 0.85, 1.25). Higher HCSD scores, indicating higher levels of distrust, were associated with lower odds of

sharing and intent to share genomic results with family members (OR=0.15, 95% CI: 0.03, 0.76). Scores on the HCSD did not influence discussing or intent to discuss genomic results with providers (OR=0.93, CI: 0.79, 1.09).

The results of the exploratory mediation analyses can be seen in table 4. The interaction between genetic test results and HCSD scores was excluded from the mediation analyses because it was non-significant in the preceding logistic regression models. The mediation analyses revealed a significant negative indirect effect of HCSD on familial sharing though the PRU anticipatory guidance domain (*ab*=-0.17, CI: -0.005, -0.01), with the proportion of the total effect mediated estimated to be 0.10. Similarly, there were significant negative indirect effects through PRU immediate benefit (*ab*=-0.03, CI: -0.06, -0.01) and PRU social benefit (*ab*=-0.03, CI: -0.07, -0.01). with 0.18 of the total effect of HSD on familial results sharing accounted for by the indirect effects, respectively.

4.5 Discussion

Our analyses suggest no observable relationship between medical distrust and intent to change health behavior based on genetic result. There is a significant negative relationship between medical distrust and sharing or intent to share genomic results with family members. We saw that perceived non-clinical utility of genomic medicine, as measured by the PRU domains of anticipatory guidance, immediate benefit, and social benefit mediated the relationship between mistrust and intent to share genomic information with family. Our analysis showed no association between medical distrust and discussing or intent to discuss genomic results with health care provider or patient-initiated health behavior changes.

Evidence that medical distrust is associated with lower odds of familial genomic results sharing or intent to share results suggests adults with higher medical distrust may forgo familial

genomic results sharing. Using mediation analysis, we also saw perceptions of personal utility played a role in the decision to share genomic results with family members. This pattern of results may suggest that increased personal utility beliefs undermines the negative impacts of medical distrust on familial information sharing. Perceptions of personal utility are thought to be malleable, and emphasizing the anticipatory guidance, immediate benefit, and social benefit gained by genomic sequencing may help lower the negative impact of medical distrust on familial sharing of genomic results.

Previous research has shown higher trust in physician is associated with higher rates of medical disclosure. In the current work we saw that higher medical distrust was not associated with lower likelihood of discussion or intent to discuss genomic results with providers as we had hypothesized. One possible explanation for this lack of finding is that trust and distrust are separate constructs and may interact with medical information disclosure differently. Thus, trust may engender medical disclosure, but medical distrust does not prevent it. An alternative explanation may also be that genomic results are qualitatively different from other types of medical information. Research suggests there is limited stigma associated with genomic results for heritable cancer syndromes.[103] However, disclosing your medical history related to substance abuse or sexual history carries the risk of stigmatization and may be more vulnerable to the influence of medical trust or distrust.

Approximately 20% (109 of 432) of our sample made changes or cited intent for patient-initiated health behavior change based on their genomic sequencing results. Further testing is needed to establish why there was no effect of medical distrust on patient-initiated health behavior change. This may indicate a degree of trust in genomic sequencings results even in the presence of medical distrust and could suggest that the negative impact of medical distrust may,

in part, be dependent on the medical context. Clearly, some of the participants who experienced medical distrust endorsed patient-initiated health behavior change or intent to change based on their sequencing results.

We had planned to investigate the impact of medical distrust on the participant intent to follow health care providers' medical recommendations related to their genomic sequencing results. Unfortunately, the available data was inadequate to model this outcome. The item assessing intent of follow health care recommendations was administered during the 16-week time point and was only answerable after having affirmed receiving sequencing findings positive for cancer or cancer syndromes, then listing recommended behavior changes. Due to the low rate of positive genomic finding in this sample, regular participant loss to follow up, and issues gathering data during the COVID-19 pandemic, many participants did not see or were never administered this item. Future research examining intent to follow medically recommended behavior change would benefit from moving this important outcome to earlier survey timepoints.

Previous work investigating the impact of medical distrust in medical genetic sequencing has primarily focused on the impact it has on self-reported willingness to participate in research or receive medical sequencing. This research is often conducted using focus groups who are not offered sequencing as part of the research. The sample recruited for CHARM utilized adults who agreed to genomic sequencing and indicated by a clinical family history-based screening. This allows greater generalization of results to populations willing to undergo sequencing, the population most likely to be encountered in clinical practice. The high degree of racial and ethnic diversity represented in this sample further enhances the generalizability of this research. With that said, it is important to understand that patients who agree to participate in genomic research may be different from those who will refuse genomic sequencing, or who would not be

comfortable participating in medical research. Further, difficulty based on retaining participants during the COVID-19 pandemic may have caused self-selection that could limit generalizability of our findings. This is exemplified by the significant racial/ethnicity status and education differences between the participants lost to follow up, and those in the complete case sample.

Our findings do suggest medical distrust can impact information sharing. Future research should continue to investigate the influence of medical distrust on this, and other health behavior outcomes associated with results of clinical genomic sequencing. This is important because the utility of genomic medicine is only realized when results of sequencing are discussed with providers, and the recommendations from those providers are acted upon.

Figure 4.1: Mediation model of the effect of patient reported utility domain on the relationship between medical distrust and Familial genomic results sharing

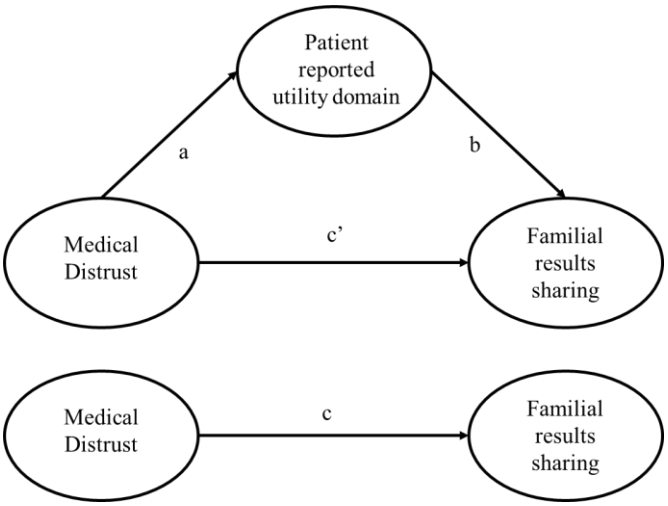


Table 4.1: Outcomes and novel items

Outcome	Novel item
Provider recommended health behavior change	Have you followed the recommendations? (sic)
Patient-initiated health behavior change	Have you made any changes in your health care or lifestyle, not based on medical recommendations made by your doctor or health care provider?
Genomic results sharing with provider	Did you discuss your genetic test results with your/your child's doctors or health care providers?
Genomic results sharing with family	Since receiving your/your child's study results, have you shared the information with any biological family members (blood relatives)?

Table 4.2: Sample characteristics and lost to follow up				
	Lost to follow up (N=349)		**Complete cases (N=431)**	
	Mean (S.D.)		**Mean (S.D.)**	
HCSD score	24.94 (6.68)		25.93 (5.71)	
Age	39.41 (7.27)		37.37 (8.64)	
	N	**%**	**N**	**%**
Gender				
Female	265	75.93	329	76.33
Male	72	20.63	94	21.86
Transgendered/non-binary	12	4	11	2.55
Education*				
High school graduate or less	94	22.69	96	18.14
post-high school training or certificate but no bachelor's degree	146	42.40	168	35.12
Bachelor's degree or graduate professional degree	117	33.52	222	40.74
Yearly Income				
$0- $39,999	146	41.83	151	35.12
$40,000 - $79,999	121	34.67	153	35.58
$80, 000 +	82	23.49	127	29.30
Race/Ethnicity*				
White or European American	148	42.40	257	59.53
Racial/Ethnic minority	201	57.29	174	40.47

HCSD= Health Care System Distrust Scale
*p<.05

Table 4.3: Impact of healthcare system distrust on results sharing and health behavior change

Domain	N	Odds ratio (S.E.)	95% C.I.
Change health behavior	432	1.04 (0.11)	0.85 to 1.25
Follow medical recommendations	9	-	-
Share with provider	431	0.93 (0.23)	0.79 to 1.09
Family communications	433	0.15 (0.13)	0.03 to 0.76*

*=p<.05
S.E.= Standard Error
95% C.I. = 95% confidence interval

Table 4.4 Mediation of the relationship between medical distrust and familial genetic information sharing by domain of personal utility

	Anticipatory guidance	Immediate benefit	Social benefit
Indirect effect	ab=-0.17, 95% CI: -0.05, -0.01*	ab=-0.03, 95% CI= -0.06, -0.01*	ab=-0.03, 95% CI: -0.07, -0.01*
Direct effect	c'=-0.15, 95% CI: -0.31, 0.01	c'=-0.12, 95% CI: -0.28, 0.05	c'=-0.15, 95% CI: -0.30, 0.01
Total effect	c=-0.17, 95% CI: -0.33, 0.01	c=-0.15, 95% CI: -0.32, -0.02*	c=-0.18, 95% CI: -0.33, -0.01*
Proportion of total effect mediated	0.10	0.18	0.18

*= p<.05
All coefficients are standardized
Confidence intervals are bias corrected

Chapter 5. Conclusions

5.1 Summary of findings

The future of medical genomics is dependent on patients are research participants. Patients who receive genomic sequencing need to gain the health benefits of preventative and precision medicine to actuarially justify the cost of implementation of medical genomic sequencing. Further progress in genomic medicine is dependent on massive reserves of participant bio-banked data for the study of genome-wide associations, polygenic risk scores and the future of precision medicine. As mine and other research has pointed out, participation in research, uptake of preventative medicine or health behavior change, and treatment adherence all may depend on lowering medical distrust.

This work attempts to understand the impact of medical mistrust on genomic medicine by substantiating a conceptual model of effect utilizing constructs and assessments designed to be specific to genomic medicine. Further, this research worked to overcome limitations previous research on distrust in genomic medicine by employing a clinical research sample of participants who agree to receive genomic sequencing as part of participation in a research study. Utilizing this sample allowed us greater validity and generalizability in our estimates of prevalence, prediction, association, and behavioral outcomes. Moreover, this approach allowed us to characterize the possible threat posed by medical distrust to outcomes related to genomic sequencing and allowed us to compare that threat to observed prevalence of medical distrust in other clinical contexts.

Another unique strength of the current research was the racial/ethnic diversity of the sample. While many genomic research studies struggle to recruit racially and ethnically diverse populations, the parent CHARM study successfully recruited a very diverse sample. With this we were able to disaggregate what would classically be a single racial/ ethnic minority variable so that we could assess patterns of predictions by more granular self-reported race/ethnicity categories including: American Indian/Native American/Native Alaskan, Black/African American, Asian/ Pacific Islander,

Hispanic/Latino, White/European American, Middle Eastern. This disaggregation is further enhanced by the presence of gender minorities, who are often not studied alongside their non-gender gendered counterparts in medical mistrust research.

The focus of this body of research was to 1) identify prevalence and patient level-sociodemographic predictors of medical distrust 2) gauge the impact of perceptions of utility of genomic medicine and feelings related to receipt of genomic screening on medical distrust, and 3) examine how medical mistrust impacts patient-initiated health behavior change related to genomic results, and if medical mistrust impacts discussion of results with health care providers and familial genomic results sharing.

The first study assessed prevalence and predictors of medical distrust in a clinical research sample of adults who had agreed to undergo whole exome sequencing after a positive screening for familial history of cancer or cancer syndromes. Findings suggested that the prevalence of medical mistrust is similar to existing prevalence estimates from different clinical context.[47] Similarly, known predictors of distrust from existing estimates held true in a genomic medicine context, with African American race/ethnicity, trans/non-binary gender identity, higher education, lower income, lower health care access and poorer mental health predicting high medical mistrust.

Our second study examined how medical mistrust impacted perceptions of perceived personal utility of genomic sequencing, and feelings about receipt of genomic results. We observed no relationship between medical mistrust and feelings about receipt of genomic results. However, we did find evidence of a significant inverse relationship between medical mistrust and perception of personal utility of genomic results across all domains of the construct: anticipatory guidance, immediate benefit, and social benefit.

The final study examined the impact of medical distrust on intent to change heath behavior outcomes including patient-initiated health behavior change, and intent to discuss or share results with health care providers and family members. No effect was observed between medical distrust and patient-initiated heath behavior or discussion of genomic results with health care providers. Our analysis did

show evidence of an effect of medical distrust on sharing genomic results with family members. We tested this relationship for mediation by perceptions of personal utility of genomics revealing an indirect pathway of effect of medical mistrust on familial genomic information sharing through all three domains of personal utility: anticipatory guidance, immediate benefit, and social benefit.

5.2 Implications

All three studies make a unique contribution to our understanding of medical distrust in genomic medicine and underscore the theory that medical distrust is an issue that care providers and researchers will need to address in the field of medical genomics. The prevalence estimate of medical distrust observed in the first paper signals that medical distrust is as prevalent in medical genetics as it is in another field of medicine.[47] Our estimate relied on a cut point established previously in a sample of adults receiving inpatient cardiac care unit. We chose this cut point because there is limited research establishing cut point for medical distrust more broadly. Having no cut point allows for easier, but somewhat subjective, interpretation of research findings in the wider literature of distrust. This does, however, limit the ability to compare conclusions across studies. An established clinical cut point would greatly benefit the field of medical distrust research.

The adapted conceptual model was largely supported by the findings of the current work. Our first study presented evidence of prediction of medical distrust based on patient-level socio-demographic, health care access, health status variables. Our ability to disaggregate racial/ethnic and gender categories allowed us to observe the how patterns of prediction of medical distrust align with patterns of historic and contemporary medical stigma. While association between medical mistrust and stigmatized and underserved populations have been witnessed before[12,19,25], this work further buttresses our understanding. Our findings provide justification for further exploration of trauma related to experiences of stigma and lack of medical access as a causal component of medical distrust. Further, this may suggest that there is a fundamental difference between the experience of medical distrust between stigmatized populations and

non-stigmatized populations that should be explored by researchers working to best operationalize this construct.

Studies two and three worked in tandem to identify constructs associated with both genomic medicine and medical distrust, gage the relationship to medical distrust and health behavior outcomes in a genomic context, and finally look at how these constructs impact the relationship between medical distrust and health behavior. Findings of these studies further support the assumptions in the conceptual model through the observed effect of distrust on familial genomic information sharing and the mediation of that relationship by the domains of personal utility. This finding of mediation between medical distrust and familial information sharing by the domains of the PRU suggests perceptions of utility undermine the negative effect of medical distrust on health behavior. This negative mediated pathway from medical mistrust, through utility perceptions, to heath behavior suggests compelling avenues for future research to lower the impact of medical mistrust.

Lack of effect witnessed in study three between medical distrust and patient-initiated health behavior change and intent to discuss genomic results with a health care provider may signal a qualitative differences in the effect of mistrust in genomic medicine. This could reflect an inherent trust in genomic results currently. Further, as suggested in chapter four, genomic results may have lower stigma associated with them than other types of medical information. If this is the case, proponents and practitioners of medical genetics may want to jealously protect the good will genomics interventions currently have. Research on public trust suggests it is easier to maintain, than restore.[104]

Finally, while the mediation witnessed in chapter four compellingly hinted at an option to address the negative impacts of medical distrust through emphasis of domains of personal utility, the proportions of those relationships were significant, but small. Taken with the results of the first study, addressing medical stigma may be easier. If experiences of stigma are conceptualized as a type of trauma, existing models of trauma informed care may lower negative impacts of medical distrust without need for additional educational or behavioral brief interventions.

5.3 Limitations

Results and interpretations derived from these data should be viewed considering important limitations. As noted previously, medical distrust is often the primary reason cited for research non-participation.[10,31,32] This means any data we have received were taken from adults who were able to overcome existing medical distrust to participate in the CHARM research study. This self-selection may limit generalizability of our results to populations who would not participate in research, or not agree to medical sequencing. Further, The PRU plays a significant role in the analysis and interpretation of these results. While our findings offer support for the construct and measure, the measure has yet to be fully psychometrically validated. The final form of this measure may be different from the version of the questions we chose to implement. Finally, the lost to follow up participants in our third study severely hinder generalization. Post-hoc testing reveals clear differences in the proportion of racial/ethnic minority adults and adults with lower educations between our complete case sample and our lost to follow up sample. This again creates a self-selecting sample of adults with the means to participate and complete a research study during the initial year of the COVID-19 pandemic. Future research may validate or invalidate the generalizability of our findings, regardless we stand by the efforts of our parent study's research staff and participants and acknowledge the difficulty of their work and contributions with unerring gratitude.

5.4 Future research

The current body of work opens several avenues for productive future research in medical distrust and genomic medicine, as well as the study of medical distrust more generally. The lack of effect in our third study was surprising. As mentioned in the conclusion this may indicate a medical-context specific effect of medical distrust. The idea that there may be a difference in distrust based on type of intervention has not been studied. Our lack of finding is not adequate to conclude this is the case, but any distinctions

regarding what medical context patients trust or distrust would allow us to better target future interventions to overcome that distrust.

The current construct of medical distrust may represent different constructs that share similar endpoints of disregard or non-engagement in medical care. Medical distrust originating from experiences of stigma or trauma may be qualitatively different than medical distrust with other origins. This is exemplified within the literature by the disagreement between survey assessments of medical distrust, some of which focus on experiences of outgroup membership, while others focus on beliefs about medicine. Firmly defining the construct, how it relates to specific populations, and establishing clear clinical cut points would be a boon to this field of research and may allow faster innovation.

Simultaneously, work is needed that continues to investigate effective interventions to address and overcome medical distrust. There are currently no effective strategies to prevent treatment hesitancy associated with medical distrust. While the current work puts forward some compelling clues for future behavioral interventions, work investigating other mediators or practice changes to undermine the negative impact of medical distrust on health behavioral outcomes should continue.

5.5 Conclusions

Results from this body of work suggest medical distrust may be as impactful to health behavior outcomes associated with genomic medicine, as it is in other medical context. While limited in this sample, there was evidence of the effect of medical distrust on outcomes associated with medical genomics. The prevalence and predictors of medical distrust are similar to those seen in other medical context[47], but genomic medicine may be more resilient to medical distrust than other fields of medicine. Further, research into the construct of medical distrust, its medical-context specific nature, and the possibility of interventions to address medical distrust are needed.

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