SOCIOCULTURAL AND ETHICAL CONSIDERATIONS FOR THE TRANSLATION OF GENOMIC HEALTH APPLICATIONS

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2015

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Program Authorized to Offer Degree:

Public Health, Health Services

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ABSTRACT

Sociocultural and Ethical Considerations for the Translation of Genomic Health Applications

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Genomic health applications are poised to play a central role in precision medicine, a tailored approach to disease prevention and treatment that accounts for individual variability in genes, environments, and lifestyles. Precision medicine is hypothesized to improve both individual and population health outcomes by personalizing health care and public health interventions. Prior examples of interventions that improved individual health, but widened outcome gaps for disadvantaged groups suggest that translating public investments in precision medicine into population health benefits requires deliberate attention to health equity. The three studies that make up this dissertation therefore explored how sociocultural factors that place individuals at risk for experiencing health disparities shape the discovery, development, delivery, and health impact of genomic health applications. The first study focused on the discovery phase, developing a six-item instrument measuring conflation of observational biospecimen-based research and clinical care for use in Latino communities, who are currently underrepresented in genomic research. The final instrument demonstrated high internal consistency, evidence of content and construct validity, and no evidence of floor and ceiling effects. It can be used in future efforts to recruit Latinos into biomedical studies. The second study focused on the development and delivery of obesity prevention and control interventions that include messages about inherited and behavioral risk factors. We described variation in beliefs about the causes of obesity (inheritance, diet, and physical activity) by ethnicity and acculturation

indicators in women enrolled in a cohort study in South King County, Washington. Results showed that Hispanic and Caucasian women held different beliefs about inheritance and physical activity's contribution to obesity; ethnic differences in genetic attributions were more pronounced than differences in physical activity attributions. Compared to Hispanic women who completed the study's baseline questionnaire in English, Hispanic women who completed it in Spanish had a higher probability of not believing at all in inheritance as a contributor to obesity. We concluded that obesity-related interventions that emphasize genetic risk factors may be less relevant to low-acculturation Hispanic women without additional tailoring. The third study focused on the delivery and health impact of genetic counseling and testing for hereditary breast and ovarian cancer and examined whether routine referral to genetic counseling could help address current disparities in utilization by education level. Study results indicated that uptake of counseling after referral did not differ by education level, nor did referral's effect on changes in genetic testing awareness and likelihood of subsequent genetic testing, which increased for all women. We concluded that systematic referral to genetic counseling may be a promising way to increase utilization of genetic services as well as address health care disparities by education level. Overall, these results help to improve our understanding of how sociocultural factors influence genomic translation. The dissertation suggests that trade-offs between effectiveness, efficiency, and equity goals are necessary to prevent intervention-generated inequalities and ensure that precision medicine approaches lead to population health benefits.

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INTRODUCTION

Genomic health interventions, namely genomic tests providing information to help diagnosis, treat, or prevent disease, have the potential to increase health care's precision and convert resulting gains in efficacy into improved population health outcomes.[1,2] This approach to disease prevention and treatment, which takes individual variability into account, falls into the larger category of tailored health interventions now commonly referred to as precision medicine.[3] Excitement about harnessing genomic and other biotechnologies to improve individual and population health through personalization is high, as evidenced by a $215 million federal Precision Medicine Initiative launched in 2015.[4,5]

During his 2015 State of the Union address President Obama described The Precision Medicine Initiative as a way, "…to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier."[4] Public health leaders have cautioned that large scale investments in genomic medicine like the Precision Medicine Initiative must include a dedicated focus on health disparities (i.e. health outcome differences closely linked to social, economic, and/or environmental disadvantage),[6] as interventions that improve individual health outcomes may also widen gaps for disadvantaged groups.[7,8] Coronary artery bypass grafts, colorectal cancer screening, and Papanicolaou testing, for example, lowered overall morbidity and mortality from coronary heart disease, colorectal, and cervical cancer in the United States, but also widened health disparities by race, ethnicity, and socioeconomic status.[9-11] Such relative outcome differences, which occur when a medical or public health interventions intended to improve the overall health of the population disproportionally benefits advantaged groups, have been termed intervention-generation inequities.[12]

This dissertation identifies ways in which genomic health applications may produce or widen health disparities through the creation of intervention-generated inequalities. It is guided by a normative model of research translational developed to help direct research towards population health-level benefits (see

Figure 1.1).[13] The model illustrates the cyclical sequence of research and development activities required for a health application to improve individual and population health outcomes. In the context of genomics, a novel association between a genetic marker and health outcome of interest must first be identified and validated in the discovery phase. Second, in the development phase, a health application—for example a genomic test providing information about drug treatment response—needs to be created and clinically evaluated in patients with the disease or trait of interest. Third, in the delivery phase, the health application must be implemented in everyday practice, typically through the creation of clinical and public health recommendations or guidelines. Evaluating the genomic health application's impact on individual and population health outcomes represents the fourth and final phase of the translational process.[14,15]

Notably, the model helps clarify how intervention-generated inequalities occur and provides guidance on how to prevent them. It shows that a genomic health application's potential to improve population health outcomes and the implications for health equity are a function of interrelated outcomes at each stage of translation. Specifically, generalizability at the discovery stage (the degree to which genomic research results can be considered broadly representative), efficacy at the development stage (how well the health application works when implemented under ideal conditions), and effectiveness at the delivery stage (how well the health application works under conditions of actual application). By calling out the need for dedicated assessment and priority setting at its center, the model also highlights that research translation is an inherently ethical activity. Value judgments made at each phase—scientific, cultural, and economic choices and potential tradeoffs between these—ultimately determine whether the development and widespread dissemination of a specific health application improves population health outcomes.[13,16]

Guided by this normative model, the three studies that make up this dissertation span the translational cycle and explore how sociocultural factors that place individuals at risk for experiencing health disparities, including ethnicity, acculturation, and education, shape the discovery, development, delivery, and health impact of genomic applications. Though the studies focus on different phases, sociocultural factors, and types of genomic health applications, they all consider ethical issue inherent to genomic translation as well as the health equity implications of the translational process as a whole. The specific

aims of each study are as follows. The first study (discovery phase) aims to develop an instrument measuring conflation of observational biospecimen research and clinical care for use with Latino communities, who are currently under-represented in genomic research studies. The resulting instrument can be used to foster informed participation decision-making in this medically underserved subpopulation. The second study (development and delivery phases) aims to describe variation in beliefs about what causes obesity between Hispanic and Caucasian women and explore acculturation's impact on obesity causal beliefs. Study results will provide information about subgroups that may respond differently to obesity prevention and control interventions that include information about inherited and behavioral risk factors and the need to develop tailored intervention approaches. Finally, the third study (delivery and outcomes phases) aims to identify differential effects of systematic referral to genetic counseling in women at high-risk of breast and ovarian cancer by education level. Study findings will provide preliminary evidence of whether this intervention approach could help to address current health care disparities in use of genetic services.

These three complementary studies are motived by an ethical commitment to preventing intervention-generated inequalities that is implicit in precision medicine's ultimate goal of improving population health. Though intervention-generated inequalities are only one of many complex factors contributing to health disparities in the US, they are particularly troubling from an ethical perspective because they result from efforts to improve health funded with public resources and promising better outcomes for all. Findings from these studies will be informative for developing and deploying genomic interventions in ways that minimize their potential to create or widen health outcome gaps for disadvantaged groups.

FOOTNOTE

[a] We use the terms Hispanic and Latino interchangeably throughout the dissertation, reflecting the language used in the original research studies and provided to participants for self-identification. The US census defines Hispanic/Latino ethnicity as persons of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race.[17]

REFERENCES

1. Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature.* 2011;470:204-13.

2. Khoury MJ, Clauser SB, Freedman AN, et al. Population sciences translational research, and the opportunities and challenges for genomics to reduce the burden of cancer in the 21st century. *Cancer Epidemiol Biomarkers Prev.* 2011;20:2105-114.

3. National Research Council. *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. Washington, DC: Nation Academies Press, 2011.

4. Collins FS, Varmus, H. A new initiative on precision medicine. *N Engl J Med.* 2015;372:793-5.

5. The White House, Office of the Press Secretary. (2015). FACT SHEET: President Obama's Precision Medicine Initiative [Press release]. Retrieved from https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative.

6. US Department of Health and Human Services. *National Healthcare Quality Report, 2012.* AHRQ Publication No. 13-0003. May 2013, Rockville, MD.

7. Dankwa-Mullan I, Bull J, Sy F. Precision medicine and health disparities: an advancing science of individualizing patient care. *Am J Public Health.* 2015;105:S368.

8. Khoury MJ, Evans JP. A public health perspective on a National Precision Medicine Cohort: balancing long-term knowledge generation with early health benefit. *JAMA.* 2015;313:2117-8.

9. Groeneveld PW, Laufer SB, Garber AM. Technology diffusion, hospital variation, and racial disparities among elderly Medicare beneficiaries 1989-2000. *Med Care.* 2005;43:320-9.

10. Irby K, Anderson WF, Henson DE, et al. Emerging and widening colorectal carcinoma disparities between blacks and whites in the United States (1975-2002). *Cancer Epidemiol Biomarkers Prev.* 2006;15:792-7.

11. Simard EP, Fedewa S, Ma J, et al. Widening socioeconomic disparities in cervical cancer mortality among women in 26 states, 1993-2007. *Cancer.* 2012;118:5110-6.

12. White M, Adams J, Heywood P. How and why do interventions that increase health overall widen inequalities within populations? In *Social Inequality and Public Health*. 2009. Bristol, UK: The Policy Press.

13. Kelley M, Edwards K, Starks H, et al. Values in translation: how asking the right questions can move translational science towards greater health impact. *Clin Trans Sci.* 2013;5:445-51.

14. Khoury MJ, Gwinn M, Yoon PM, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med*. 2007;9:665-74.

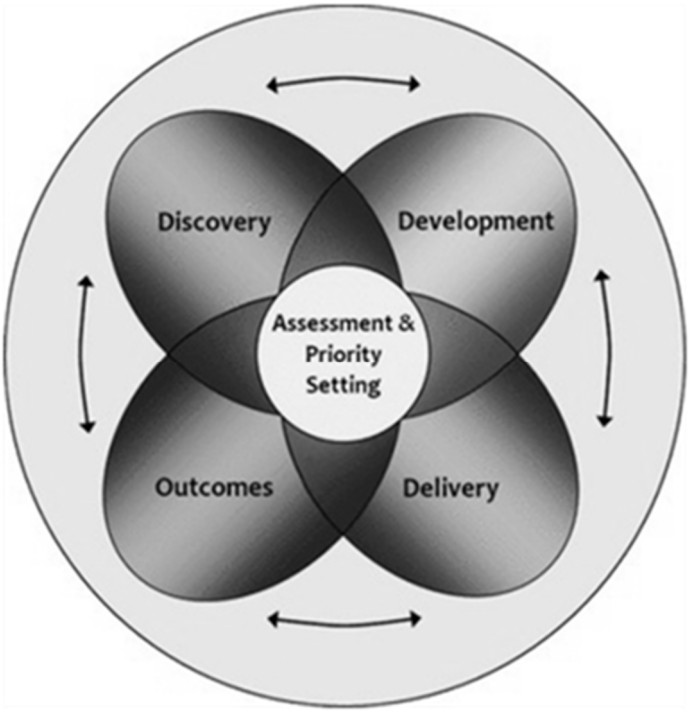
15. Chang CQ, Tingle SR, Filipski KK, et al. An overview of recommendations and translational milestones for genomic tests in cancer. *Genet Med.* 2015;17:431-40.

16. Tugwell P, de Savigny D, Hawker G, et al. Applying clinical epidemiological methods to health equity: the equity effectiveness loop. *BMJ.* 2006;332:358-61.

17. Humes KR, Jones NA, Ramirez RR. *Overview of race and Hispanic origin: 2010.* Washington, DC: US Census Bureau. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Published 2012. Accessed May 7, 2015.

FIGURES

Figure 1.1: Normative model of research translation guiding dissertation specific aims.



Note. From Kelley et al., 2012.

-Chapter 2-

GIVING SAMPLES OR "GETTING CHECKED": MEASURING CONFLATION OF OBSERVATIONAL BIOSPECIMEN RESEARCH AND CLINICAL CARE IN LATINO COMMUNITIES

INTRODUCTION

Observational studies relying on biological samples are increasingly used to better understand disease with a goal of improving population health. Though personalized results from biospecimen-based studies are not often clinically actionable and thus not made available to participants, prior research indicates that expectations of receiving meaningful health information as a fringe benefit of sample donation are not uncommon.[1,2] Expectations of personal health benefit in the context of observational research have been termed diagnostic misconception[3], a variant of the therapeutic misconception that occurs in clinical trials when research participants either misunderstand or fail to appreciate key distinctions between the goals and guiding principles of research and clinical care[4,5].

Our research group encountered a number of beliefs related to diagnostic misconception while conducting a qualitative study about observational biospecimen-based research participation with Latinos living on the United States (US)-Mexico border.[6] Our participants reported that they were extremely willing to provide biological samples for research, including blood, urine, stool, saliva, and buccal cells, but often equated providing a sample for research with undergoing a clinical evaluation. Sample donation was described as, '…a way of doing our check-ups to see if we're in time to [detect] diseases'. [6] The conflation of research and clinical care influenced participants' perceptions of the potential benefits of sample donation, which included receiving individualized information about medical diagnoses and future disease risk. Additionally, participants had trouble grasping the nature of observational research and were more familiar with clinical studies involving medical interventions.

Diagnostic misconception has important ethical dimensions, as inaccurate beliefs about the research process may unduly influence decisions to take part in research and impact the quality of the informed

consent process.[7] Ethical concerns are magnified for Latino populations, who face substantial barriers to accessing health care in the US[8], but are increasingly sought after as research participants to improve generalizability, particularly in genomic studies.[9,10] Factors influencing Latinos' participation in studies involving the collection of biologic samples and accompanying phenotypic information have not been well studied.[11,12] Whether expectations of receiving personally meaningful health information as a fringe benefit of participation drive sample donation in a coercive manner is particularly unclear.

In an effort to enable identification of beliefs related to diagnostic misconception in Latino communities, this study developed and validated a quantitative instrument measuring conflation of observational biospecimen-based research and clinical care. The availability of such an instrument will allow future research exploring the origins and consequences of diagnostic misconception and help facilitate ethically informed recruitment efforts in medically underserved communities.

METHODS

Conceptual model and item development

The conceptual model used to guide instrument development was informed by a review of the literature on biospecimen donation and diagnostic misconception, prior qualitative research conducted by our group on the US-Mexico border, and a quantitative measure of therapeutic misconception developed by Appelbaum et al.[13] Common misconceptions about research with biological samples that were documented literature or observed in our prior work were grouped into three related domains. The first domain considers understanding of the distinctions between observational biospecimen-based research and clinical trials. The second and third domains are modeled on dimensions of the therapeutic misconception scale.[13] Specifically, the second domain concerns understanding of the purpose of biospecimen-based research, i.e. identifies the degree of conflation of the goals of biological sample collection for research (creating generalizable knowledge) and the goals of sample collection in clinical care (informing the care of the individual patient). The third domain concerns perceptions of the likelihood of receiving personal benefits in the form of individualized health information when providing a biospecimen for research.

We developed six items for the first domain and seven for the second and third. Items were written based on meaningful themes and quotations from our prior interviews and focus groups as well as relevant items developed for the therapeutic misconception scale.[13] Items were measured on 4-point Likert-like scales from strongly agree to strongly disagree. Based on our prior experience working with Latino communities, we did not include 'do not know' as a response option because of respondents' tendency to choose this option rather than make a potentially incorrect guess. Each item's reading level was assessed in English using the Flesch-Kincaid grade level formula and kept as low as possible.[14] Items were reviewed for face-validity in English by two community-based participatory researchers who work extensively with Latino communities and three experts in measurement development. Items were then pre-tested in English (n=5) and Spanish (n=5) with members of the target population using standard cognitive interviewing techniques.[15] Interviews were conducted by a certified translator trained in cognitive interviewing, who also conducted all study translations.

Field-testing

The instrument administered for field-testing included final versions of all items written for each domain along with single items assessing prior sample donation for research ('yes', 'no', or 'don't know') and likelihood of providing a sample for research in the future ('very likely', 'somewhat likely', or 'not likely'). We described biological samples as materials taken from the human body, including tissues like skin, hair, nails, cheek cells and fluids like blood, urine, or salvia. Scientific research was described as a method of learning about health and how to prevent and treat diseases. The definitions were based on the National Cancer Institutes' (NCI) Cancer 101 module on biospecimens and biobanking.[16] We also administered the Genetic Knowledge Index[17] (GKI) and Hall et al.'s scale measuring trust in medical researchers[18] along with standard demographic and health care access questions. The five-item version of the GKI has been previously used to assess basic knowledge about genetics in the general population.[19] Participants indicated whether five statements were true or false and a total score from zero to five was calculated from their number of correct responses (Cronbach's alpha = 0.56). The four-item version of Hall et al.'s scale measuring trust in medical researchers, which has shown high reliability in national surveys, was modified for administration by removing the 'do not know/can't answer' response

option and changing ‘medical researcher’ to ‘scientists who do research with biological samples’ and ‘doctor’ to ‘scientist’. The items were measured on 4-point Likert-like scales from strongly disagree to strongly agree and summed, with higher overall scores indicating more trust in researchers (Cronbach’s alpha: 0.52).

We used a targeted recruitment strategy to obtain a sample of 150 self-identified Latino adults with an equivalent gender distribution to complete the survey instrument. Our sample size was chosen to provide adequate power for exploratory factor analyses (EFA) [20]. Recruitment efforts relied on a National Cancer Institute (NCI) Community Networks Program Center (CNPC) based in Sunnyside, Washington with strong connections to the Latino community there. Latinos living in this area of Eastern Washington, called the lower Yakima Valley, are almost exclusively from Mexico and are similar to Latinos living on the border with respect to income, acculturation, education, and health care access.[6,11,21] Recruitment and survey administration were conducted by two CNPC staff members who are residents of the lower Yakima Valley and fluent in both English and Spanish. Study participants completed the surveys in person at community events, CNPC- sponsored health fairs, and local shopping facilities. Study materials were available in both English and Spanish and participants could use whatever language they felt most comfortable with. The survey was verbally administered, with participants also having their own copy to read if they desired, and took approximately 15-20 minutes to complete. This study was reviewed by the University of Washington Institutional Review Board who declared it exempt from ethics approval. Participants received a $15 gift-card as a thank you for their time. Completed surveys were periodically checked by the study team to ensure data quality and consistency in administration. When recruitment was completed the survey data was reviewed, coded, and entered into Stata 13 software.[22] A random sample of surveys (25%) was reviewed to confirm the quality of entered data.

Data analysis

Response distributions were examined for each item, with items coded so that higher scores indicated increasing misconceptions about research with biological samples. EFA was used to determine if items intended to measure the same domain were inter-correlated and to inform item selection for the final

instrument.[23] We used the principal components factor method followed by Promax rotation, both implemented using the 'factor' command in Stata 13.[24,25] Promax rotation was chosen to be consistent with our conceptual model, which proposed that the three domains were interrelated.[26]

In the initial factor extraction, six factors had eigenvalues above one and most items loaded onto the first factor. The remaining items were spilt so that those assessing accurate and inaccurate perceptions of biospecimen-based research loaded onto separate factors, suggesting that the observed factor structure may have been due to item wording and re-coding. The scree plot test had two changes in slope or "elbows", one that occurred after the third factor and one that occurred after the sixth. [27] Based on these findings, we pursued two models moving forward. The first retained three factors aligning with the three domains originally proposed in our conceptual model. The second model retained one factor and reflected the overall degree of conflation of biospecimen research and clinical care. Rotated factor loadings from these models were used to create two reduced versions of the instrument (termed the three-factor and the one-factor solutions). For both models, items that had loadings above 0.60 on their own factor (and under 0.40 on any other factor for the three-factor solution) were included in the final instrument. A second EFA was conducted on both reduced instruments and factor loading are reported for these analyses.

Item-to-scale correlations and Cronbach's alpha statistics were calculated for both the one- and three-factor solutions. Additionally, mean subscores for each dimension in the three-factor solution and their correlation with the total score were calculated along with Cronbach's alpha statistics. To assess construct validity correlations with the GKI and Hall et al.'s scale measuring trust in medical researchers were examined. In our qualitative work on the US-Mexico border individuals who knew the least about research were often the most trusting of researchers and willing to provide biospecimens. Thus, we hypothesized that increasing misconceptions about biospecimen-based research as measured by the three-factor solution would be negatively correlated with genetic knowledge and positively correlated with researcher trust. Subscores for all three domains would follow the same patterns, with the exception of lay understanding of research, which would be uncorrelated with researcher trust. Similarly, we

hypothesized that increasing conflation of research with biological samples and clinical care as measured by the one-factor solution would be negatively correlated with genetic knowledge and positively correlated with researcher trust.

RESULTS

Participants

Descriptive characteristics for the cognitive interview and survey participants are shown in Table 2.1. Participants reflected the demographic profile of Latinos living in the lower Yakima Valley, with most having a high school education or less, an annual household income under $35,000, and either government health insurance (Medicare, Medicaid, or coupons) or no health insurance.

Instrument psychometrics

The 20 piloted items are presented by domain in Supplemental Tables 2.1-2.3 (see Appendix) along with item-level response data. Missing responses were rare and always occurred at the end of each domain. Responses in all domains tended to be skewed towards 'strongly agree' and 'agree', regardless of whether the item assessed accurate or inaccurate perceptions of biospecimen research. More than half the respondents 'agreed' or 'strongly agreed' with 67% of the lay understanding items, 86% if the purpose items, and 100% of the benefits items.

Two of the items were highly skewed and excluded from the EFA. The Kaiser-Meyer-Olkin (KMO) statistic for the remaining 18 items was 0.77 and Barlett's test of sphericity rejected the null hypothesis, indicating underlying data structure sufficient for EFA.[26] Table 2.2 provides factor loadings and correlations with domain scores and total scores for the eight items retained in the three-factor solution. The first factor (benefits) accounted for 33.9% of item variance, the second factor (purpose) accounted for 20.3%, and the third (lay understanding) accounted for 18.3%. Items included in the three-factor solution had high loadings on their own factor and high correlations with domain scores. But, correlations with the total score and Cronbach's alphas were low for the lay understanding and purpose domains. Alpha statistics were 0.550 for lay understanding, 0.511 for purpose, 0.808 for benefits, and 0.589 for the overall eight-

item scale. Table 2.3 provides factor loadings and correlations with total scores for the six items retained in the one-factor solution. The first factor accounted for 56.7% of item variance and Cronbach's alpha statistic for the six-item scale was 0.844.

Instrument validity

Results for the analyses examining construct validity are given in Table 2.4. For the thee-factor solution, purpose subscores were uncorrelated with genetic knowledge and negatively correlated with researcher trust, while total scores were uncorrelated with research trust, contradicting our *a priori* hypotheses. Total scores for the one-factor solution assessing conflation of biospecimen-based research and clinical care were negatively correlated with genetic knowledge and positively correlated with researcher trust as hypothesized.

As the one-factor solution had superior psychometric properties and evidence of construct validity, we examined differences in the degree of conflation of biospecimen-based research and clinical care by demographic, health care access, and research participation characteristics using *t*-tests and one-way analysis of variance (ANOVA). These results are presented in Table 2.5. Conflation of research and clinical care differed significantly by employment status, primary language spoken, health insurance type, usual source of health care, and self-rated health. Individuals who were unemployed, spoke only Spanish, had no health insurance, received care at non-traditional venues, and had good self-rated health received higher scores, indicating greater conflation of biospecimen-based research and clinical care. Scores were inversely associated with years of education (test for linear trend, p-value < 0.008).

DISCUSSION

We successfully developed a six-item instrument measuring conflation of observational biospecimen-based research and clinical care for use in Latino communities. The final instrument demonstrated high internal consistency, evidence of content and construct validity, and no evidence of floor and ceiling effects in a convenience sample of 150 Latino adults. It is important to note that the instrument was

developed and field-tested in community samples, not exclusively with prior biospecimen donors. Diagnostic misconception can be stringently understood as misconceptions about the likelihood of receiving personal health-related information as a part of research participation in individuals who have provided informed consent and donated a biological sample.[2] Thus, we believe our instrument is best described as assessing conflation of observational biospecimen-based research and clinical care, not diagnostic misconception. Still, this is one of the first quantitative instruments with demonstrated reliability and validity available to measure beliefs related to diagnostic misconception in potential biospecimen donors. Documenting the instrument's performance characteristics in biospecimen donors, who may differ from potential donors, will allow the instrument to be used at multiple time-points throughout the research process.

Our conceptual model proposed three domains of misconceptions: lay understanding of the distinction between observational biospecimen-based research and clinical trials, understanding of the purpose of biospecimen-based research, and perceived likelihood of personal benefit. This model is similar to the theoretical framework used by Appelbaum et al. to develop their measure of therapeutic misconception, but with unreasonable beliefs about the degree of individualization of the intervention replaced by understanding of the distinction between clinical and observational research.[13] Our analysis did not confirm the three domains proposed in our conceptual model. Two features likely account for the three-factor solution's poor psychometric properties. First, many of the items written for the 'purpose' and 'lay understanding' subscales were dropped due to double loading in the EFA. Thus, these subscales were comprised of only two items and had poor internal consistency.[28] Second, respondents' tendency to 'agree' or 'strongly agree' with most items, regardless of whether they reflected accurate or inaccurate perceptions of biospecimen-based research, caused response patterns for these two types of items to vary. That two domains were comprised of all inaccurate items (lay-understanding and benefits), while one was comprised of all accurate items (purpose), also contributed to poor reliability. It is likely that a multidimensional instrument comprised of all accurate or all inaccurate items would have had improved psychometric characteristics. The therapeutic misconception scale, for example, contains all inaccurate statements, despite piloting both accurate and inaccurate items.[13] It is possible that if we had developed

and piloted a larger number of items for each domain our ability to distinguish between distinct beliefs related to diagnostic misconceptions would have improved. Alternatively, our conceptual model may be inaccurate or incomplete. Additional theoretical work defining diagnostic misconception and clarifying its manifestation is needed to guide develop of a multidimensional measure.

Latinos are projected to make up 31% of the US population by 2060[29], but currently lack robust representation in clinical research funded by the National Institutes of Health as well as large scale biomarker and other in vitro studies that use de-identified biological samples.[30,31] A growing body of research indicates, however, that Latinos are highly willing to provide biospecimens for research.[11,12,32,33] Eighty four percent of our sample was 'very' or 'somewhat' likely to provide a sample for research in the future. There is evidence from other populations that individuals may participate in therapeutic and non-therapeutic research as way to monitor their health and access otherwise unavailable health services.[34,35] Thus, concern that conflation of research participation and clinical evaluation may drive biospecimen donation in medically underserved Latino communities was a primary motivation for this study.

Conflation of biospecimen-based research and clinical care as measured by our instrument did not differ by self-reported willingness to participate in biospecimen research in our sample ($p=0.144$). Still, we found that Latino subgroups facing the most substantial barriers to accessing high quality health care had higher scores, indicating a greater degree of conflation. Those who were unemployed, spoke only Spanish, had no health insurance, and received health care outside of traditional venues were more likely to conflate aspects of research and clinical care. These groups stand to face a disproportionate burden of the potential harms resulting from diagnostic misconception, which may include damaged trust in both doctors and researchers.[5]

Efforts to recruit Latinos into biospecimen-based research must avoid paternalism, but also recognizing that biospecimen donation is not without risk. Additional research is needed to determine whether Latinos' with limited access to traditional health care experience undue influence in the research setting and the role that diagnostic misconception plays in this process. While mean scores did not differ between those

who reported prior biospecimen donation in a one-way ANOVA, individuals who reported providing a sample for research in the past tended to have lower scores than those who had not (15.75 vs. 17.11) and a corresponding non-parametric test was significant (Kruskal-Wallis p-value < 0.031). Thus, it is possible the recruitment and informed consent process may help clarify misconceptions about the purpose and benefits of observational research compared to clinical care. Alternatively, those with access to research participation opportunities may be more knowledgeable about research. These are questions that should be assessed in future longitudinal studies with biospecimen donors.

This study had several limitations. We surveyed Mexican-Americans living in a rural, agricultural community using non-probability sampling, limiting the generalizability of our findings to other Hispanic and Latino communities in the US. A recent focus group study with Puerto Ricans living in Buffalo, New York with similar income, education, and health care access characteristics to our participants reported that "the inability to conceptualize the difference between biomedical research and medical diagnostic services and results" was common.[32] This suggests that our results may have broader applicability across Latino subpopulations. The instruments used for validation had poor internal consistency in our population, which could have affected our results. Additionally, we did not assess item ordering effects, reproducibility, or responsiveness of the survey instrument. Our instrument can be easily implemented in other settings to examine these properties. Because a gold standard does not exist, we could not assess criterion validity. Also, because we did not include a 'do not know' option we are unable to tell if participants misunderstood the question, did now know enough about research to make an educated guess, or truly had misperceptions about research with biological samples. Results from a recent effort to develop a biobanking knowledge scale in South Florida suggest that almost half of respondents respond 'do not know' to knowledge items.[36] Finally, we did not establish the interpretability of our instrument by assigning qualitative meaning to quantitative scores. Understanding the degree of conflation that could compromises participation decision-making and establishing cut-off scores identifying groups at risk of experiencing diagnostic misconception during the recruitment and informed consent process will be an important goal for future studies.

Conclusion

The availability of a quantitative instrument measuring conflation of research with biological samples and clinical care will enable researchers to better flesh out how rural Latinos make decisions to participate in biospecimen-based research in a context of health care inequality. The final 6-item survey instrument can be used to assess baseline knowledge and beliefs about biospecimen-based research to guide community engagement activities prior to recruitment or to evaluate educational interventions or the quality of the informed consent process. Efforts to improve public health through large-scale biospecimen-based studies are predicated on investigators' ability to engage diverse populations. It is imperative that attempts to increase Latinos' representation in population-based biobanking research do not inadvertently exploit this community's limited access to clinical services and desire for health information.[37] A better understanding of diagnostic misconception will help ensure that decisions to donate biospecimens are made based on an informed weighing of the current risks and benefits of research participation.

REFERENCES

1. Halverson MA, Ross LF. Incidental findings of therapeutic misconception in biobank-based research. *Genet Med*. 2012;14:611-615.

2. Nobile H, Vermeulen E, Thys K, Bergmann MM, Borry P. Why do participants enroll in population biobank studies? *Expert Rev Mol Diagn.* 2012;13:35-47.

3. Clayton EW, Ross LF. Implications of disclosing individual results of clinical research. *JAMA.* 2006;295:37-38.

4. Appelbaum PS, Roth LH, Lidz CW. The therapeutic misconception: informed consent in psychiatric research*. Int J Law Psych*. 1982;5:319-329.

5. Lidz CW, Appelbaum PS. The therapeutic misconception: problems and solutions. *Med Care.* 2002;40:V55-V63.

6. Ceballos R, Knerr S, Scott MA, Hohl SD, Malen RC, Vilchis H, et al. Latino beliefs about biomedical research participation: a qualitative study on the US-Mexico border. *J Empir Res Hum Res Eth.* 2014;9:10-21.

7. Beskow LM, Dombeck CB, Thomspon CP, Watson-Ormond JK, Weinfurt KP. Informed consent for biobanking: consensus-based guidelines for adequate comprehension. *Genet Med*. 2015;17:226-233..

8. Ortega AN, Fang H, Perez VH, Rizzo JA, Carter-Pokras O, Wallace SP, et al. Health care access, use of services, and experiences among undocumented Mexicans and other Latinos. *Arch Intern Med.* 2007;167:2354-2360.

9. Fullerton SM. The input-output problem: whose DNA do we study, and why does it matter? In: Burke W, Edwards KA, Goering S, Holland S, Trinidad SB, editors. *Achieving justice in genomic translation: rethinking the pathway to benefit*. New York: Oxford University Press, 2011. p. 40-55.

10. Thompson B, Hebert JR. Involving disparate populations in clinical trials and biobanking protocols: experiences form the Community Network Program Centers. *Cancer Epidemiol Biomarkers Prev.* 2014;23:370-373.

11. Hohl SD, Gonzalez C, Carosso E, Ibarra G, Thompson B. "I did it for us and I would do it again": perspectives of rural Latinos on providing biospecimens for research. *Am J Public Health*. 2014;104:911-916.

12. Lopez DS, Fernandez ME, Cano MA, Mendez C, Tsai CL, Wetter DW, et al. Association of acculturation, nativity, and years living in the United States with biobanking among individuals of Mexican descent. *Cancer Epidemol Biomarkers Prev*. 2014;23:402-408.

13. Appelbaum PS, Anatchkova M, Albert K, Dunn LB, Lidz CW. Therapeutic misconception in research subjects: development and validation of a measure. *Clin Trials*. 2012;9:748-761.

14. Kincaid JP, Fishburne RP, Rogers RL, Chissom BS. *Derivation of New Readability Formulas (Automated Readability Index, Fog Count, and Flesch Reading Ease formula) for Navy Enlisted Personnel*. Research Branch Report 8-75. Chief of Naval Technical Training: Naval Air Station Memphis, 1975.

15. Nápoles-Springer AM, Santoyo-Olsson J, O'Brien H, Stewart AL. Using cognitive interviews to develop surveys in diverse populations. *Med Care*. 2006;44:S21-S30.

16. Hill TG, Briant KJ, Bowen D, Boerner V, Vu T, Lopez K, et al. Evaluation of Cancer 101: an educational program for native settings. *J Canc Educ*. 2010;25:329-336.

17. Furr LA, Kelly SE. The Genetic Knowledge Index: developing a standard measure of genetic knowledge. *Genet Test*. 1999;3:193-199.

18. Hall MA, Camacho F, Lawlor JS, DePuy V, Sugarman J, Weinfurt K. Measuring trust in medical researchers. *Med Care*. 2006;44:1048-53.

19. Ashida S, Goodman M, Pandya C, Koehly LM, Lachance C, Stafford, J, et al. Age differences in genetic knowledge, health literacy and causal beliefs for health conditions. *Public Health Genomics.* 2011;14:307-316.

20. Terwee CB, Bot SDM, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol.* 2007;60:34-42.

21. U.S. Census Bureau; generated by Sarah Knerr using American FactFinder. Available at: http://factfinder2.census.gov. Accessed 4 December 2014.

22. StataCorp. 2012. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

23. Comfry AL. Factor-analytic methods of scale development in personality and clinical psychology. J *Consult Clin Psychol*. 1988;56:754-761.

24. Preacher KJ, MacCallum RC. Repairing Tom Swift's electric factor analysis machine. *Understanding Statistics*. 2003;2:13-43.

25. de Vet HCW, Ader HJ, Terwee C, Pouwer F. Are factor analytic techniques used appropriately in the validation of health status questionnaires? A systematic review on the quality of factor analyses of the SF-36. *Qual Life Res*. 2005;14:1203-1218.

26. Tabachnick BG, Fidell LS. *Using Multivariate Statistics,* 6th ed. Saddle River, NJ: Pearson, 2013.

27. Cattell RB. The scree test for the number of factors. *Multivariate Behav Res.* 1966;1:245–276.

28. Steiner DL. Starting at the beginning: an introduction to coefficient alpha and internal consistency. *J Pers Assess.* 2003;80:99-103.

29. U.S. Census Bureau, 2012*. U.S. Census Bureau projections show a slower growing, older, more diverse nation a half century from now*. Available at: https://census.gov/newsroom/ releases/archives/ populations/cb12-243.html. Accessed 4 December 2014.

30. Bustamante CD, Burchard EG, De La Vega FM. Genomics for the world. *Nature.* 2011;475:163-165.

31. Department of Health and Human Services (DHHS), 2013. *Monitoring of adherence to the NIH policy on the inclusion of women and minorities as subjects in clinical research.* Fiscal Year 2011-2012. Available at: http://orwh.od.nih.gov/research/inclusion/reports.asp. Accessed 4 December 2014.

32. Rodriguez EM, Torres ET, Erwin DO. Awareness and interest in biospecimen donation for cancer research: views from gatekeepers and prospective participants in the Latino community. *J Community Genet.* 2013;4:461-468.

33. Sanderson SC, Difenbach MA, Zinberg R, Horozitz CR, Smirnoff M, Zweig M, et al. Willingness to participate in genomics research and desire for personal results among underrepresented minority patients: a structured interview study. *J Community Genet*. 2012;4:469-482.

34. Kirkland SA, Raina PS, Woflson C, Strople G, Kits O, Dukeshire S, et al. Exploring the acceptability and feasibility of conducting a large longitudinal population-based study in Canada. *Can J Aging*. 2009; 28:231-242.

35. Townsend A, Cox SM. Accessing health services through the back door: a qualitative interview study investigating reasons why people participate in health research in Canada. *BMC Med Ethics*. 2012;14:40.

36. Wells KJ, Arevalo M, Mead CD, Gwede CK, Quinn GP, Luque JS, et al. Development and validation of the biobanking attitudes and knowledge scale (BANKS). *Cancer Epidemiol Biomarkers Prev.* 2014;23:374-383.

37. Fisher JA, Kalbaugh CA. Challenging assumptions about minority participation in US clinical research. *Am J Public Health.* 2011;101:2217-2222.

TABLES

Table 2.1: Cognitive interview and survey participant characteristics.

		Interview N	Survey N, %
Overall		10	150
Age (Mean, SD)		31.6, 10	38.8, 15
Gender	Female	7	75, 50
Employment	Full-time	8	68, 45
	Part-time	0	30, 20
	Unemployed	2	52, 35
Years education	≤ 4	1	20, 13
	5-8	1	39, 26
	9-12	2	75, 50
	≥ 13	6	16, 11
Annual household income	<$15,000	0	63, 42
	$15,000 -$34,999	4	71, 47
	$35,000 -$49,999	2	13, 9
	>$50,000	4	3, 2
Primary language spoken	Only Spanish	2	38, 25
	Spanish better than English	1	36, 24
	Both	3	39, 26
	English better than Spanish	4	32, 21
	Only English	0	5, 3
Health insurance	Private	7	30, 20
	Government	2	77, 51
	Both	0	5, 3
	None	1	38, 25
Usual source of Care	Doctor's office	4	41, 27
	Clinic	6	97, 65
	Hospital	0	6, 4
	Other[a]	0	6, 4
Has regular doctor	Yes	5	112, 75
Self-rated health	Excellent or very good	2	51, 34
	Good	2	65, 43
	Fair or poor	5	34, 23
	Don't know	1	0, 0
Provided a sample for research in the past	Yes	4	16, 11
	No	4	129, 86
	Don't know	2	5, 3
Would provide a sample for research in the future	Very likely	7	58, 39
	Somewhat likely	3	72, 48
	Not likely	0	20, 13

Notes: Numbers may not sum to 100 due to rounding error.

[a]Other: Pharmacy, traditional medicine/sobadores, family/friends, or prefer not to answer.

Table 2.2: Final scale characteristics for three-factor solution.

Item	Mean (SD)	Factor Loadings			Correlation with domain score[d]	Correlation with total score[d,e]
		B[a]	LU[b]	P[c]		
1. A person must go to the hospital to give a biological sample for scientific research.[f]	2.10 (0.73)		0.710		0.826	0.614
2. A person must be invited by a doctor to give a biological sample for scientific research.[f]	2.50 (0.79)		0.860		0.837	0.464
3. Scientific research using biological samples is done to learn about what causes disease, not about each person who gives a biological sample.	1.89 (0.64)			0.863	0.855	0.047
4. A scientific researcher's number one goal is to learn more about how to fight disease.	1.63 (0.54)			0.743	0.784	0.145
5. Researchers will always tell people if their biological sample shows risk for disease.[f]	3.01 (0.71)	0.699			0.718	0.561
6. One reason to give a biological sample for scientific research is to get a medical checkup.[f]	2.59 (0.76)	0.748			0.790	0.726
7. One reason to give a biological sample for scientific research is to find out if you have a disease.[f]	2.91 (0.67)	0.852			0.826	0.645
8. Information you get by giving a biological sample for scientific research is the best information about your health you could get.[f]	2.90 (0.76)	0.820			0.854	0.721

Notes: Cells empty if <0.400, SD=standard deviation.

[a]Benefits: Mean domain score (SD)=11.40 (2.32); [b]Lay Understanding: Mean domain score (SD)= 5.09 (1.30); [c]Purpose: Mean domain score (SD)=3.52 (0.97); [d]Pearson product moment; [e]Mean total score (SD)= 20.11 (2.88); [f]Item reverse coded.

Table 2.3: Final scale characteristics for one-factor solution.

Item	Mean (SD)	Factor Loadings	Correlation with total score[a,b]
1. A scientific researcher's number one job is to make sure that the research helps each person who gives a biological sample.[c]	2.88 (0.76)	0.647	0.670
2. Researchers mostly do scientific research using biological samples to tell people who give samples if they are sick.[c]	2.77 (0.79)	0.773	0.776
3. Researchers will always tell people if their biological sample shows risk for disease.[c]	3.01 (0.71)	0.654	0.663
4. One reason to give a biological sample for scientific research is to get a medical checkup.[c]	2.59 (0.76)	0.779	0.774
5. One reason to give a biological sample for scientific research is to find out if you have a disease.[c]	2.91 (0.67)	0.823	0.806
6. Information you get by giving a biological sample for scientific research is the best information about your health you could get.[c]	2.90 (0.76)	0.823	0.811

Notes: SD=standard deviation.

[a]Pearson product moment; [b]Mean total score (SD)= 17.05 (3.35); [c]Item reverse coded.

Table 2.4: Validation results.

	Correlate	Coefficient for three-factor solution[a]	A priori expectation	Coefficient for one-factor solution[a]	A priori expectation
Lay Understanding	GKI	-0.300	Yes		
	Trust	-0.002	Yes		
Purpose	GKI	0.151	No		
	Trust	-0.321	No		
Benefits	GKI	-0.365	Yes		
	Trust	0.330	Yes		
Total Scale	GKI	-0.361	Yes	-0.381	Yes
	Trust	0.147	No	0.381	Yes

Notes: GKI=Genetic Knowledge Index; Trust=Hall et al.'s scale measuring trusting medical researchers.

[a]Pearson product-moment.

APPENDIX

Supplementary Table 2.1: Item-level data for domain one of piloted survey instrument.

Domain	Item	Frequency					Mean	SD
			1	2	3	4	Missing	
Lay understanding	1. A person must be sick to give a sample for scientific research.[a]	n	21	89	32	8	0	2.18	0.73
		%	14.0	59.3	21.3	5.3	0		
	2. A person is not required to take medicine when giving a biological sample for scientific research.	n	19	64	57	10	0	2.39	0.79
		%	12.7	42.7	38.0	6.7	0		
	3. A person must go to the hospital to give a biological sample for scientific research.[a]	n	9	48	73	20	0	2.69	0.78
		%	6.0	32.0	48.7	13.3	0		
	4. A healthy person can give a biological sample for scientific research.	n	50	92	7	1	0	1.73	0.58
		%	33.3	61.3	4.7	0.7	0		
	5. A person must be invited by a doctor to give a biological sample for scientific research.[a]	n	13	63	58	45	1	2.50	0.79
		%	8.7	42.0	38.7	10.0	0.7		
	6. Scientific research using biological samples is mainly done to test if new medical treatments are safe for humans.[a,b]	n	4	16	95	33	2	3.06	0.66
		%	2.7	10.7	63.3	22.0	1.3		

Notes: SD=standard deviation; Response categories: 1= strongly agree; 2=agree; 3=disagree; 4=strongly disagree.

[a]Items were reverse coded, so that a higher score indicates presence of a misconception; [b]Skewed item.

Supplementary Table 2.2: Item-level data for domain two of piloted survey instrument.

Domain	Item	Frequency						Mean	SD
			1	2	3	4	Missing		
Purpose	1. The purpose of scientific research using biological samples is to give the best medical information to those who give samples.[a]	n	0	20	99	31	0	3.07	0.58
		%	0	13.3	66.0	20.7	0		
	2. Scientific research using biological samples is done to help the people who give samples, not to help future generations.[a]	n	20	58	57	15	0	2.45	0.85
		%	13.3	38.7	38.0	10.0	0		
	3. A scientific researcher's number one job is to make sure that the research helps each person who gives a biological sample.[a]	n	6	35	80	29	0	2.88	0.76
		%	4.0	23.3	53.3	19.3	0		
	4. Researchers mostly do scientific research using biological samples to tell people who give samples if they are sick.[a]	n	7	47	70	26	0	2.77	0.79
		%	4.7	31.3	46.7	17.3	0		
	5. Scientific research using biological samples is done to learn about what causes disease, not about each person who gives a biological sample.	n	38	93	17	2	0	1.89	0.64
		%	25.3	62.0	11.3	1.3	0		
	6. The goal of scientific research with biological samples is help people in the future, whether or not it helps each person who gives a sample.[b]	n	50	89	9	2	0	1.75	0.62
		%	33.3	59.3	6.0	1.3	0		
	7. A scientific researcher's number one goal is to learn more about how to fight disease.	n	59	86	4	0	1	1.63	0.54
		%	39.3	57.3	2.7	0	0.7		

Notes: SD=standard deviation; Response categories: 1= strongly agree; 2=agree; 3=disagree; 4=strongly disagree.

[a]Items were reverse coded, so that a higher score indicates presence of a misconception; [b]Skewed item.

Supplementary Table 2.3: Item-level data for domain three of piloted survey instrument.

Domain	Item	Frequency						Mean	SD
			1	2	3	4	Missing		
Benefits	1. Researchers will always tell people if their biological sample shows risk for disease.[a]	n	4	25	87	34	0	3.01	0.71
		%	2.7	16.7	58.0	22.7	0		
	2. Giving a biological sample for scientific research may not give you any important information about your health.	n	19	69	54	8	0	2.34	0.77
		%	12.7	46.0	36.0	5.3	0		
	3. One reason to give a biological sample for scientific research is to get a medical checkup.[a]	n	11	54	71	14	0	2.59	0.76
		%	7.3	36.0	47.3	9.3	0		
	4. By giving a biological sample for scientific research, a person will always get important information about their disease risk.[a]	n	3	28	93	26	0	2.94	0.66
		%	2.0	18.7	62.0	17.3	0		
	5. When you give a biological sample for scientific research you always learn if you might get the disease they are studying.[a]	n	2	36	92	20	0	2.87	0.64
		%	1.3	24.0	61.3	13.3	0		
	6. One reason to give a biological sample for scientific research is to find out if you have a disease.[a]	n	5	26	96	23	0	2.91	0.67
		%	3.3	17.3	64.0	15.3	0		
	7. Information you get by giving a biological sample for scientific research is the best information about your health you could get.[a]	n	5	36	77	31	1	2.90	0.76
		%	3.3	24.0	51.3	20.7	0.7		

Notes: SD=standard deviation; Response categories: 1= strongly agree; 2=agree; 3=disagree; 4=strongly disagree.

[a]Items were reverse coded, so that a higher score indicates presence of a misconception.

-Chapter 3-

VARIATION IN WOMEN'S BELIEFS ABOUT WHAT CAUSES OBESITY: THE ROLE OF ETHNICITY AND ACCULTURATION

INTRODUCTION

Obesity's increasing prevalence in the United States (US) is now recognized as an epidemic with social, financial, and health consequences.[1,2] Particular attention has been given to obesity's disproportionate burden in Hispanics (whom the census defines as persons of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race), due, in part, to the their rapid demographic growth.[3-5] Gaps between Hispanic and Caucasian women are particularly striking. Recent data indicates a 9.2% difference in the age-adjusted prevalence of obesity between these groups (41.4% vs. 32.2% in women over the age of 20), highlighting the need for interventions to reduce these disparities.[1]

Obesity's underlying causes are complex—genetic, environmental, and behavioral factors interact to determine weight-status.[6] Individuals' beliefs about the causes of health conditions like obesity (causal attributions) are a key determinant of how they conceptualize and respond to health threats.[7,8] Understanding obesity causal beliefs in Hispanic and Caucasian women—particularly genetic causal beliefs—will be essential for informing the next generation of targeted, tailored, and personalized obesity prevention and treatment approaches.[9-11] In prior work, Sanderson et al. found no differences in obesity causal beliefs between Hispanics and non-Hispanics of any race, though participants were from a single clinic and all spoke English.[12] Hispanics were 61% more likely to believe that obesity is caused by overeating and not exercising (hold behavioral attributions) than Caucasians in the 2007 Health Information National Trends Survey (HINTS), while the belief that obesity is inherited (genetic attributions) did not vary by ethnicity.[13]

Clarifying the influence of acculturation (the convergence of heritage and receiving cultural practices, values, and identifications) on obesity attributions is also important, particularly in Hispanic women, who

are more likely to be recent immigrants.[14] Ethnic identity does not directly cause variation in causal beliefs, but is associated with other characteristics that shape disease attributions.[15] These characteristics also track with acculturation and include demographic and psychosocial factors like health status, access to and understanding of health information, social norms, and cultural/folk beliefs.[14,16] Research indicating that differences in obesity attributions by nativity, but not ethnicity, remain after accounting for age, gender, body mass index (BMI), and race[17] suggests that acculturation could be a stronger predictor of obesity causal beliefs than Hispanic ethnicity and may explain inconsistent results from prior studies exploring ethnic variation in obesity causal beliefs.

The objective of the present study was to describe variation in beliefs about the causes of obesity between Hispanic and Caucasian women enrolled in a cohort study in Washington State. The secondary aim was to investigate acculturation's role in shaping obesity attributions in Hispanic women.

METHODS

Participants

Data came from the baseline visit of the Socioeconomic Status and Obesity Study (SESO)—a longitudinal cohort study of Hispanic and Caucasian women living in South King County, Washington. SESO was approved by the University of Washington Institutional Review Board and women were recruited from 2010 to 2011 using a population-based multi-stage sampling method. Groups of houses in 143 randomly chosen block-groups with a high representation of Hispanic, low education, and low income households based on 2000 census data were approached by female study staff to determine residency of eligible women (Hispanic or Caucasian, aged 30-50 years, fluent in English or Spanish, and planning to remain in the area). For households with multiple eligible women the respondent with the most recent birthday was invited to participate. Participants provided written informed consent, completed a baseline pen and paper survey in their choice of English or Spanish, and had their height and weight measured. Of the approximately 22,000 addresses approached, 1,018 women were eligible and enrolled in the cohort. The present study was restricted to women who were not currently pregnant (n=1,002).

Measures

All variables, with the exception of BMI, were self-reported in the baseline survey.

Obesity causal beliefs

Obesity causal beliefs were assessed using questions modeled on HINTS 2007, but measuring behavioral attributions separately.[18] To measure genetic causal beliefs individuals were asked, "To what extent do you believe that obesity is inherited," with response options falling on a 4-point Likert-type scale ("don't believe at all", "believe a little", "believe quite a bit", and "believe a lot"). Attributions for lifestyle behaviors were assessed similarly, asking: "To what extent do you believe that obesity is caused by not eating a healthy diet" and "To what extent do you believe that obesity is caused by not exercising regularly". A healthy diet was defined as eating plenty of fruits and vegetables and not too much sugar or fatty foods. Exercising regularly was defined as planned physical activity done to increase physical fitness at least 3 times a week.

Demographic factors

Participants self-reported "Hispanic origin such as Mexican American, Latin American, Puerto Rican or Cuban" (yes or no) and were categorized as underweight/normal weight; overweight; or obese/severely obese based on height and weight data collected at baseline.[19]

Participants provided their date of birth and highest level of education from 1 ("no schooling" completed) to 16 ("doctoral degree"). Age was dichotomized (30 - < 40 vs. 40 - ≤51) and education was defined as: high school degree or less; some college/associate degree; or Bachelor's/advanced degree. Employment status was measured by asking, "What is your current job status?" Responses were dichotomized (not working vs. working full- or part-time). Women reported whether they currently had health insurance of any type (yes or no).

Psychosocial factors

Questions reflecting social norms of weight, diet, and physical activity were developed based on research investigating the spread of obesity in social networks.[20] Participants were asked how many of their five closest friends and how many of their five closest family members "…are overweight?" Responses could range from 0-5 and were averaged to provide a single social norms score. Norms for diet and physical activity were assessed by asking how many of their five closest friends and family members "…eat a healthy diet" and "…exercise regularly?"

Efficacy and outcome expectations for weight control, diet, and physical activity were measured using single questions.[21] Efficacy expectations for weight control were assessed by asking: "How sure are you that you will control your weight over the next year?" Response options fell on a 0-10 scale from "not sure" to "very sure". Outcome expectations were measured by asking: "Do you believe being overweight is harmful to your health?" Response options were on a 0-10 scale from "not at all harmful" to "very harmful". Expectancies for diet and physical activity asked about perceived ability to "eat less sugar and fat" and "exercise regularly" over the next year and the perceived harm of not doing so.

Acculturation factors

Acculturation was conceptualized as the adoption of US cultural practices, values, and identifications. Nativity (born in the US or abroad) and the language participants chose to complete the survey (English or Spanish) were used as proxies of acculturation.[14]

Statistical Analysis

Summary statistics were calculated for all variables overall and by ethnicity. Differences in obesity causal beliefs by ethnicity and by nativity and survey language in Hispanic women were examined in bivariate analyses.

Marginal effect estimates obtained from multinomial logistic regression models were used to assess the relationship between ethnicity and obesity causal beliefs.[22] Multinomial logistic regression was used

instead of ordered logistic regression because the proportional odds assumption that the relationship between increasing causal belief categories is equivalent was violated. Multinomial logistic regression does not constrain the relationship between causal belief categories and uses maximum likelihood estimation to calculate the log-odds of endorsing a given causal belief category compared with a reference category. To generate marginal effects the probability of endorsing a particular causal belief category (not believing “at all”, believing “a little”, believing “quite a bit", or believing “a lot” in the role of inheritance, diet, or physical activity) was estimated for each woman in the sample, treating them first as if they were Hispanic (fixing ethnicity to 1) and then as if they were Caucasian (fixing ethnicity to 0). The difference between these two predicted probabilities was calculated for each individual (giving the marginal effect of ethnicity for that individual) and differences were averaged across the sample to give the marginal effect of ethnicity, overall. Marginal effect estimates can be interpreted as comparisons of the probability of endorsing particular causal beliefs categories between hypothetical populations of Hispanic and Caucasian women with identical values of all other variables included in the model used to generate the predictions (i.e. between otherwise comparable populations). To see how differences in casual beliefs changed after accounting for potential intermediate variables, marginal effects were computed from unadjusted models and models adjusted in a step-wise fashion for demographic factors, psychosocial factors, and nativity. Competing causal beliefs were considered psychosocial factors.

Marginal effects for nativity (comparing those born abroad with those born in the US) and survey language (comparing those who completed the survey in Spanish with those who completed it in English) were estimated in Hispanic women following similar procedures. All analyses were conducted in 2015 using Stata version 13 software. Marginal effects were calculated with the margins post-estimation command using the delta method to compute standard errors and excluding women with missing data.[22]

RESULTS

Descriptive Results

Sample descriptive characteristics are provided in Table 3.1. More Hispanic women were in the younger age group, high school graduates or less, not working, uninsured, and obese/severely obese, relative to

Caucasian women. On average, Hispanic women had more family and friends who they perceived as overweight and fewer who they perceived as eating a healthy diet and exercising regularly. Hispanic women had lower mean efficacy for weight control, but higher mean outcome expectations. Mean efficacy and outcome expectancies for diet were higher in Hispanic women compared to Caucasian women, but mean physical activity expectancies were lower. Eighty three percent of Hispanic women were born outside of the US, mainly in Mexico, compared to 5% of Caucasian women. Nineteen percent of Hispanic women and all Caucasian women chose to complete the baseline survey in English.

Genetic and physical activity causal beliefs about obesity differed between Hispanic and Caucasian women based on chi-squared tests of independence ($p \leq 0.001$ for both comparisons), but diet causal beliefs did not ($p \leq 0.15$). Within Hispanic women, only genetic causal beliefs differed by nativity and survey language ($p \leq 0.001$ for both comparisons).

Marginal Effects

Table 3.2 gives marginal effect (ME) estimates for ethnicity, describing differences in the probability of endorsing particular categories of genetic and physical activity causal beliefs between Hispanic and Caucasian women. As diet causal beliefs did not vary by ethnicity in multinomial models, marginal effects were non-significant and are not presented. Hispanic ethnicity was consistently associated with a higher probability of not believing “at all” and a lower probability of believing “a little” and “quite a bit” in inheritance’s role in causing obesity. Hispanic women’s probability of reporting no role for inheritance in causing obesity was 33% higher than Caucasian women’s in an unadjusted model (95% CI: 0.28, 0.38; $p \leq 0.001$). Ethnic differences in genetic causal beliefs narrowed, but remained statistically significant, after adjusting for demographic and psychosocial factors. Only the difference in Hispanic and Caucasian women’s probability of not believing “at all” in inheritance as a cause of obesity remained significant after accounting for nativity (ME=0.12, 95% CI: 0.02, 0.22; $p \leq 0.02$). Regression coefficients from the fully adjusted multinomial logistic regression model of genetic causal beliefs are given in Supplemental Table 3.1 (Appendix).

Hispanic ethnicity was consistently associated with a higher probability of not believing “at all” and a lower probability of believing “quite a bit” in physical activity’s role in causing obesity. Hispanic women’s probability of reporting no role for physical activity in causing obesity was 5% higher than Caucasian women’s in an unadjusted model (95% CI: 0.02, 0.07; p≤0.001). The marginal effect of ethnicity on women’s probability of endorsing this outcome did not meaningfully change after adjusting for demographic factors, psychosocial factors, and nativity. Differences in the probability of believing “quite a bit” in physical activity’s role in causing obesity also remained after adjusting for demographic and psychosocial factors, but were no longer significant after accounting for nativity. Regression coefficients from the fully adjusted multinomial logistic regression model of physical activity causal beliefs are given in Supplemental Table 3.2.

Table 3.3 gives marginal effect estimates for acculturation factors in Hispanic women, describing differences in the probability of endorsing particular categories of genetic causal beliefs between those born abroad and those born in the US as well as those who completed the survey in Spanish and those who completed it in English. Diet and physical activity causal beliefs did not vary by acculturation factors in multinomial models and marginal effects are not presented for these outcomes. Hispanic women who were born abroad had a 34% higher probability of not believing “at all” in inheritance as a cause of obesity, not accounting for demographic factors, psychosocial factors, or survey language (95% CI: 0.26, 0.43; p≤0.001). These women also were less likely to believe “a little” and “quite a bit” in the role of inheritance than their US-born counterparts. Adjusting for demographic and psychosocial factors somewhat narrowed differences in genetic causal beliefs by nativity and they were no longer statistically significant after accounting for survey language.

Completing the baseline survey in Spanish (as opposed to English) was consistently associated with a higher probability of not believing “at all” and a lower probability of believing “quite a bit” in inheritance’s role in causing obesity. Adjustment for demographic factors, psychosocial factors, and nativity did not appreciably change differences in Hispanic women’s probability of endorsing these outcomes by survey language. In the fully adjusted model, women who completed the baseline survey in Spanish had a 32%

higher probability of not believing “at all” and a 38% lower probability of believe “quite a bit” in inheritance as a cause of obesity than women who completed the survey in English (95% CI: 0.18, 0.47; p≤0.001 & 95% CI: -0.56, -0.20; p≤0.001, respectively). Regression coefficients from the fully adjusted model of genetic causal beliefs in Hispanic women are given in Supplemental Table 3.3.

DISCUSSION

These findings indicate that Hispanic and Caucasian women in this sample held different beliefs about the contribution of inheritance and physical activity, but not diet, to causing obesity. Ethnic differences in genetic attributions were more pronounced than differences in physical activity attributions. Furthermore, genetic, but not diet or physical activity attributions, were associated with acculturation in Hispanic women and contributed to variation in obesity causal beliefs by ethnicity.

These results have important implications for the development and delivery of obesity-related interventions. First, messages about behavioral causes of obesity will be, for the most part, similarly relevant to Caucasian and Hispanic women. This finding is supported by a growing body of research indicating that most Hispanics, including recent immigrants, recognize the importance of diet and exercise for preventing obesity and suggesting that interventions focus on facilitating these behaviors in the US environment, rather than re-emphasizing their importance.[23-25] For a small proportion of Hispanic women additional education about the significance of regular physical activity for weight-regulation will be necessary. Extrapolating from our data, there are roughly 925,216 Hispanic women (and 752,397 Caucasian women), nationally, who see no role for physical activity in causing obesity.[26] Adjusting for demographic factors, psychosocial factors, and nativity did not meaningfully change, and in some cases increased, the marginal effect of ethnicity on physical activity causal beliefs. Future work is needed to identify underlying causes of ethnic differences in physical activity attributions.

Second, medical and public health interventions that include information about genetic determinants of obesity and/or provide personalized risk estimates based on family health history or genetic variation will likely be perceived differently by Hispanic women with different degrees of acculturation. Though much

attention has been given to interventions that integrate this type of risk information, it is unclear how effective they are for facilitating obesity prevention and control[27,28], making it difficult to predict the larger implications for obesity disparities. Still, these findings highlight future challenges for the implementation of precision medicine approaches, though access barriers for Hispanic women are perhaps of greater concern.[29] The language women chose for completing paperwork or questionnaires (a proxy for English language proficiency) may help identify those in need of additional attention during conversations about inherited risk of obesity, including the return of genetic and genomic test results.[30.31]

The substantial difference in genetic causal beliefs by acculturation in Hispanic women is this study's most novel finding. As shown in Figure 3.1, more acculturated Hispanic women had genetic causal beliefs similar, though not equivalent, to Caucasians. Genetic attributions did not differ by nativity in Caucasian women (Pearson X^2, $p \leq 0.11$), though this is a less meaningful indicator of acculturation in this group. Identifying whether differences in genetic causal beliefs by acculturation exist for other conditions (e.g. mental illness, cancer) and in other immigrant groups should be the focus of future research. Finally, the possibility that increasing recognition of obesity's genetic determinants accompanying adoption of US cultural values and practices may compound Hispanic women's internalized blame for obesity or characterize ethnic differences in obesity rates as "essential" or "pre-determined" warrants attention.[23,32,33]

Limitations

This study had a number of limitations. First, the sample had limited diversity, minimizing the generalizability of our results. Findings should be confirmed in men and Hispanic individuals with different socio-demographic profiles and countries of origin. Second, analyses were cross-sectional and should be interpreted as descriptive and not causal. Third, a number of single-item measures were used, leading to incalculable alphas. Finally, it is possible that women interpreted "inheritance" in different ways and that this question did not reflect beliefs about that role that genetic factors play in causing obesity. This measure of genetic attributions has been used in prior studies, most notable HINTS, and was piloted in both English and Spanish-speaking individuals, helping to minimize this concern.

Conclusion

Despite these limitations, the results highlight the importance of considering variation in obesity causal beliefs when undertaking obesity prevention and control efforts in diverse populations. Providing accurate and culturally appropriate education about obesity's multifactorial causes during the delivery of medical and public health interventions will help ensure that efforts to address the obesity epidemic do not exacerbate disparities.

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trend in the distribution of body mass index among US adults, 1999-2010. *JAMA.* 2012;307:491-7.

2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA*. 2012;307:483-60.

3. US Census Bureau. *US Census Bureau projections show a slower growing, older, more diverse nation a half century from now.* Washington, DC: US Census Bureau. https://census.gov/newsroom /releases/archives/populations/cb12-243.html. Published 2012. Accessed May 7, 2015.

4. Humes KR, Jones NA, Ramirez RR. *Overview of race and Hispanic origin: 2010.* Washington, DC: US Census Bureau. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Published 2012. Accessed May 7, 2015.

5. The National Hispanic Caucus of State Legislators (NHCSL). *Hispanic obesity: an American crisis.* Washington, DC: NHCSL. http://www.nhcsl.org/issues/healthcare/Hispanic-Obesity-An-American-Crisis.pdf. Published 2010. Accessed May 7, 2015.

6. Hofker M, Wijmenga C. A supersized list of obesity genes. *Nat Genet.* 2009;41:139-40.

7. Marteau TM, Weinman J. Self-regulation and the behavioural responses to DNA risk information: a theoretical analysis and framework for future research. *Soc Sci Med*. 2006;62:1360-8.

8. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness beahviour. In: LD Cameron & H Leventhal, eds. *The Self-Regulation of Health and Illness Behaviour.* New York, NY: Routledge; 2003:42-65.

9. Collins FS, Varmus H. A new initiative on precision medicine. *NEJM.* 2015;372:793-5.

10. Kreuter MW, Lukwago SN, Bucholtz DC, Clark EM, Sanders-Thompson V. Achieving cultural appropriateness in health promotion programs: targeted and tailored approaches. *Health Education Research.* 2003;30:133-146.

11. Kreuter MW, Wray RJ. Tailored and targeted health communication: strategies for enhancing information relevance. *Am J Health Behav*. 2003;24:S227-32.

12. Sanderson SC, Diefenbach MA, Streicher SA, et al. Genetic and lifestyle causal beliefs about obesity and associated diseases among ethnically diverse patients: a structured interview study. *Public Health Genomics.* 2013;16:83-93.

13. Wang C, Coups EJ. Causal beliefs about obesity and associated health behaviors: results from a population-based survey. *Int J Behav Nutr Phys Act.* 2010;7:19.

14. Schwartz SJ, Unger JB, Zamboanga BL, Szapocznik J. Rethinking the concept of acculturation: implications for theory and research. *Am Psychol*. 2010;65:237-51.

15. Kaufman JS, Cooper RS. Commentary: considerations for use of racial/ethnic classification in etiologic research. *Am J Epidemiol.* 2001;154:291-8.

16. Shiloh, S. Illness representations, self-regulation, and genetic counseling: a theoretical review. *J Genet Couns*. 2006;15:325-37.

17. Ashida S, Goodman M, Pandya C, et al. Age differences in genetic knowledge, health literacy, and causal beliefs for health conditions. *Public Health Genomics*. 2011;14:307-316.

18. Cantor D, Coa K, Crystal-Mansour S, et al. *Health Information National Trends Study (HINTS) 2007: final report.* Bethesda, MD: National Cancer Institute. http://hints.cancer.gov/docs/HINTS2007FinalReport.pdf. Published 2009. Accessed May 7, 2015.

19. National Heart Lung and Blood Institute (NHLBI). *Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults, NIH Publication No. 98-4083*. Bethesda, MD: National Institutes of Health; 1998.

20. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. *N Engl J Med*. 2007;357:370-9.

21. Grembowski D, Patrick D, Diehr P, et al. Self-efficacy and health behavior among older adults. *J Health Soc Behav*. 1993;34:89-104.

22. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. *Stata J*. 2012;12:308-331.

23. Greenhalgh S, Carney MA. Bad biocitiens?: Latinos and the US “obesity epidemic”. Hum Organ 2014;73:267-76.

24. Agne AA, Daubert R, Munoz ML, Scarinci I, Cherrington AL. The cultural context of obesity: exploring perceptions of obesity and weight loss among Latina immigrants. *J Immigr Minor Health.* 2012;14:1063-70.

25. Hoke MM, Timmerman GM, Robbins LK. Explanatory models of eating, weight, and health in rural Mexican American women. *Hisp Health Care Int*. 2006;4:143-51.

26. US Census Bureau; American Community Survey, 2013 American Community Survey 1-Year Estimates; generated by Sarah Knerr, using American FactFinder; <http://factfinder2 .census.gov>; (15 June 2015).

27. McBride CM, Bryan AD, Bray MS, Swan GE, Green ED. Health behavior change: can genomics improve behavioral adherence? *Am J Public Health.* 2012;102:401-5.

28. Marteau TM, French DP, Griffin SJ, et al. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviors. *Cochrane Database of Syst Rev.* 2010;10:1-27.

29. Tuckson RV, Newcomer L, De Sa JM. Accessing genomic medicine: affordability, diffusion, and disparities. *JAMA*. 2013;309:1469-70.

30. Afable-Munsuz A, Liang S, Ponce NA, Walsh JME. Acculturation and colorectal cancer screening among older Latino adults: differential associations by national origin. *J Gen Intern Med*. 2009;24:963-70.

31. Lee S, Nguyen HA, Tsui J. Interview language: a proxy measure for acculturation among Asian Americans in a population-based survey. *J Immigr Minor Health*. 2009;13:244-52.

32. Phelan JC, Link BG, Feldman NM. The genomic revolution and beliefs about essential racial differences: a backdoor to eugenics? *Am Sociol Rev*. 2013;78:167-91.

33. Condit C, Bates B. How lay people respond to messages about genetics, health, and race. *Clin Genet.* 2005;68:97-105.

TABLES

Table 3.1: Participant demographic, psychosocial, and acculturation characteristics and causal beliefs about obesity, by ethnicity.

	Overall (n=1,002)	Caucasian (n=493)	Hispanic (n=509)
Demographic Factors, n (%)			
Age			
30 - <40 years	566 (56.5)	259 (52.5)	307 (60.3)
40 - ≤51 years	406 (40.5)	228 (46.3)	178 (35.0)
Missing	30 (3.0)	6 (1.2)	24 (4.7)
Education			
High school graduate or less	492 (49.1)	103 (20.9)	389 (76.4)
Some college/associate degree	216 (21.6)	147 (29.8)	69 (13.6)
Bachelor's/advanced degree	294 (29.3)	243 (49.3)	51 (10.0)
Employment status			
Working full-time or part-time	568 (56.7)	326 (66.1)	242 (47.5)
Not working	428 (42.7)	165 (33.5)	263 (51.7)
Missing	6 (0.6)	2 (0.4)	4 (0.8)
Health insurance status			
Insured	539 (53.8)	406 (82.4)	133 (26.1)
Uninsured	437 (43.6)	84 (17.0)	353 (69.4)
Missing	26 (2.6)	3 (0.6)	23 (4.5)
Body mass index			
<25.0 kg/m^2 (underweight/normal weight)	259 (25.9)	186 (37.7)	73 (14.3)
25 - <30.0 kg/m^2 (overweight)	306 (30.5)	109 (22.1)	197 (38.7)
≥ 30.0 kg/m^2 (obese/severely obese)	437 (43.6)	198 (40.2)	239 (47.0)
Psychosocial Factors, n (%)			
Social norms for weight			
[Mean ± SD]	2.1 ± 1.2	2.0 ± 1.2	2.2 ± 1.3
Missing	43 (4.3)	9 (1.8)	34 (6.7)
Social norms for diet			
[Mean ± SD]	2.3 ± 1.5	2.9 ± 1.3	1.7 ± 1.5
Missing	53 (5.3)	11 (2.2)	42 (8.3)
Social norms for physical activity			
[Mean ± SD]	2.3 ± 1.3	2.7 ± 1.2	1.9 ± 1.4
Missing	59 (5.9)	11 (2.2)	48 (9.4)
Weight control efficacy expectations			
[Mean ± SD]	6.0 ± 2.6	6.1 ± 2.4	5.9 ± 2.7
Missing	3 (0.3)	1 (0.2)	2 (0.4)
Weight control outcome expectations			
[Mean ± SD]	7.6 ± 1.9	7.4 ± 1.7	7.7 ± 2.0
Missing	4 (0.4)	0 (0)	4 (0.8)
Diet efficacy expectations			
[Mean ± SD]	5.7 ± 2.9	5.6 ± 3.0	5.9 ± 2.9
Missing	6 (0.6)	3 (0.6)	3 (0.6)
Diet outcome expectations			

[Mean ± SD]	8.9 ± 1.7	8.7 ± 1.6	9.2 ± 1.7
Missing	4 (0.4)	2 (0.4)	2 (0.4)
Physical activity efficacy expectations			
[Mean ± SD]	6.7 ± 3.0	7.1 ± 2.7	6.4 ± 3.1
Missing	7 (0.7)	0 (0)	7 (1.4)
Physical activity outcome expectations			
[Mean ± SD]	7.5 ± 3.0	7.8 ± 2.4	7.2 ± 3.4
Missing	6 (0.6)	0 (0)	6 (1.2)
Acculturation Factors, n (%)			
Survey language			
English	590 (58.9)	493 (100.0)	97 (19.1)
Spanish	412 (41.1)	0 (0)	412 (80.9)
Nativity			
Born in US	530 (52.9)	467 (94.7)	63 (12.4)
Born abroad	446 (44.5)	24 (4.9)	422 (82.9)
Missing	26 (2.6)	2 (0.4)	24 (4.7)
Obesity Causal Beliefs, n (%)			
Diet attributions			
Don’t believe at all	27 (2.7)	10 (2.0)	17 (3.3)
Believe a little	94 (9.4)	43 (8.7)	51 (10.0)
Believe quite a bit	378 (37.7)	202 (41.0)	176 (34.6)
Believe a lot	497 (49.6)	236 (47.9)	261 (51.3)
Missing	6 (0.6)	2 (0.4)	4 (0.8)
Physical activity attributions			
Don’t believe at all	36 (3.6)	6 (1.2)	30 (5.9)
Believe a little	121 (12.1)	55 (11.2)	66 (13.0)
Believe quite a bit	355 (35.4)	201 (40.8)	154 (30.3)
Believe a lot	483 (48.2)	230 (46.7)	253 (49.7)
Missing	7 (0.7)	1 (0.2)	6 (1.2)
Genetic attributions			
Don’t believe at all	224 (22.4)	29 (5.9)	195 (38.3)
Believe a little	377 (37.6)	237 (48.1)	140 (27.5)
Believe quite a bit	297 (29.6)	180 (36.5)	117 (23.0)
Believe a lot	95 (9.5)	45 (9.1)	50 (9.8)
Missing	9 (0.9)	2 (0.4)	7 (1.4)

Table 3.2: Ethnicity marginal effects for genetic and physical activity causal beliefs about obesity.

	Ethnicity marginal effect estimates[a]							
	Genetic causal beliefs				Physical activity causal beliefs			
	Model 1[b] (n=993)	Model 2[c] (n=937)	Model 3[d] (n=869)	Model 4[e] (n=855)	Model 1[b] (n=995)	Model 2[c] (n=939)	Model 3[d] (n=869)	Model 4[e] (n=855)
Don't believe at all, %	**0.33*** **	**0.26*** **	**0.24*** **	**0.12***	**0.05*** **	**0.07*** **	**0.06*** **	**0.05***
(SE)	**(0.02)**	**(0.03)**	**(0.04)**	**(0.05)**	**(0.01)**	**(0.02)**	**(0.02)**	**(0.02)**
Believe a little, %	**-0.20*** **	**-0.15 *** **	**-0.14** **	-0.05	0.02	0.00	0.02	-0.01
(SE)	**(0.03)**	**(0.04)**	**(0.04)**	(0.06)	(0.02)	(0.03)	(0.03)	(0.04)
Believe quite a bit, %	**-0.13*** **	**-0.12** **	**-0.12 ** **	-0.11	**-0.10*** **	**-0.17*** **	**-0.10***	-0.09
(SE)	**(0.03)**	**(0.04)**	**(0.04)**	(0.06)	**(0.03)**	**(0.04)**	**(0.04)**	(0.06)
Believe a lot, %	0.00	0.01	0.01	0.04	0.04	**0.11***	0.02	0.04
(SE)	(0.02)	(0.02)	(0.03)	(0.04)	(0.03)	**(0.04)**	(0.04)	(0.06)

Notes: Results bolded when p≤0.05. Columns may not sum to zero due to rounding error.

[a] Reference group=Caucasian.
[b] Unadjusted (included only ethnicity).
[c] Adjusted for demographic factors (age, education, employment, health insurance, BMI).
[d] Adjusted for demographic factors and psychosocial factors (competing causal beliefs, social norms, outcome expectations, efficacy expectations).
[e] Adjusted for demographic factors, psychosocial factors, and nativity.

* p≤0.05; ** p≤0.01; *** p≤0.001

Table 3.3: Acculturation marginal effects for genetic causal beliefs about obesity in Hispanic women.

Genetic causal beliefs	Survey language marginal effect estimates[a]				Nativity marginal effect estimates[b]			
	Model 1[c] (n=502)	Model 2[d] (n=456)	Model 3[e] (n=406)	Model 4[f] (n=392)	Model 1[c] (n=479)	Model 2[d] (n=441)	Model 3[e] (n=392)	Model 4[f] (n=392)
Don't believe at all, %	**0.36*** **	**0.35*** **	**0.35*** **	**0.32*** **	**0.34*** **	**0.30*** **	**0.31*** **	0.12
(SE)	**(0.04)**	**(0.05)**	**(0.05)**	**(0.07)**	**(0.04)**	**(0.05)**	**(0.06)**	(0.13)
Believe a little, %	**-0.12***	-0.03	-0.04	0.06	**-0.17***	-0.10	**-0.16***	-0.19
(SE)	**(0.05)**	(0.06)	(0.07)	(0.08)	**(0.07)**	(0.07)	**(0.08)**	(0.12)
Believe quite a bit, %	**-0.20*** **	**-0.29*** **	**-0.30*** **	**-0.38*** **	-0.11	**-0.15***	-0.13	0.08
(SE)	**(0.05)**	**(0.07)**	**(0.08)**	**(0.09)**	(0.06)	**(0.08)**	(0.08)	(0.07)

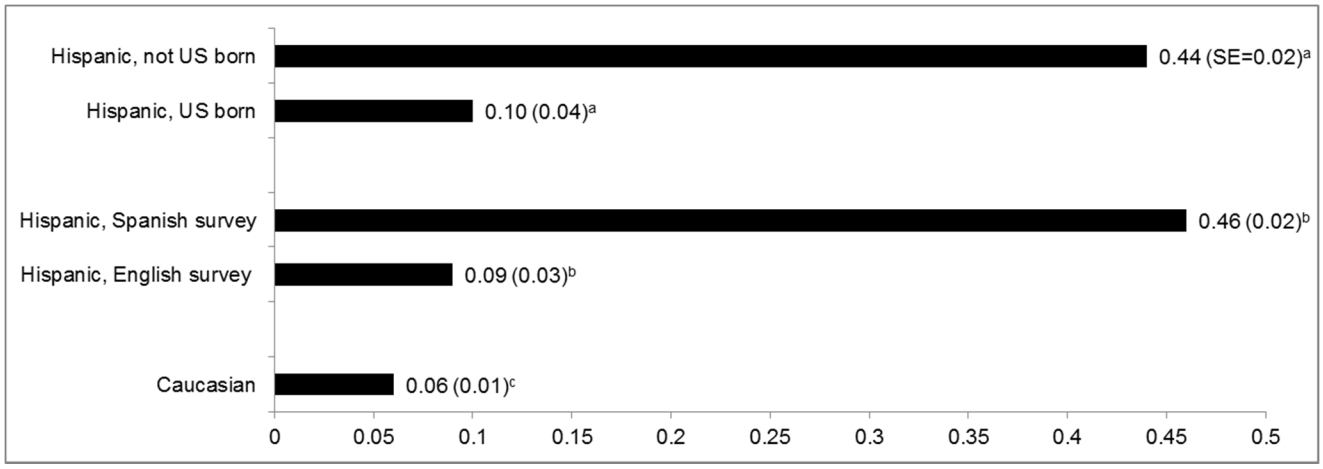
Notes: Estimates bolded when p≤0.05. Marginal effects for believe "a lot" were all non-significant and are not shown.

[a] Reference group=English.
[b] Reference group=US born.
[c] Unadjusted (included only survey language or nativity).
[d] Adjusted for demographic factors (age, education, employment, health insurance, BMI).
[e] Adjusted for demographic factors and psychosocial factors (competing causal beliefs, social norms, outcome expectations, efficacy expectations).
[f] Adjusted for demographic, psychosocial, and acculturation factors (nativity, survey language)

* p≤0.05; ** p≤0.01; *** p≤0.001

FIGURES

Figure 3.1: Predicted probability of not believing “at all” in inheritance as a cause of obesity from multinomial logistic regression models, by ethnicity and acculturation factors.



Notes: US=United States; SE=standard error

[a] Unadjusted (included only nativity) in Hispanics only, n=479
[b] Unadjusted (included only survey language) in Hispanics only, n=502
[c] Unadjusted (included only ethnicity), n=993

APPENDIX

Table S 3.1: Multinomial logistic regression model of physical activity causal beliefs about obesity adjusted for demographic factors, psychosocial factors, and nativity (n=855).

Variable (REF)	Adjusted OR (95% CI)[a]		
	Don't believe at all	Believe quite a bit	Believe a lot
Ethnicity (Caucasian)	**7.02 (1.25, 39.59)***	0.80 (0.32, 1.93)	1.13 (0.46, 2.78)
Age (40 - ≤51)	2.02 (0.78, 5.28)	1.51 (0.92, 2.48)	1.12 (0.67, 1.87)
BMI[b]			
Overweight	0.31 (0.09, 1.10)	0.88 (0.46, 1.70)	0.99 (0.50, 1.97)
Obese or severely obese	0.49 (0.15, 1.57)	0.97 (0.50, 1.85)	1.27 (0.64, 2.51)
Education[c]			
Some college or associate degree	0.91 (0.26, 3.23)	0.73 (0.37, 1.48)	0.84 (0.41, 1.73)
Bachelor's or advanced degree	0.34 (0.07, 1.61)	0.58 (0.28, 1.20)	0.61 (0.29, 1.28)
Employment status (employed)	0.93 (0.34, 2.42)	1.19 (0.72, 1.95)	1.20 (0.71, 2.01)
Health insurance status (insured)	**3.69 (1.20, 11.37)***	0.81 (0.44, 1.49)	0.92 (0.49, 1.74)
Diet causal beliefs[d]	0.72 (0.42, 1.24)	1.28 (0.94, 1.74)	**3.14 (2.22, 4.44)*****
Genetic causal beliefs[d]	0.75 (0.45, 1.25)	0.92 (0.70, 1.21)	0.95 (0.72, 1.26)
Social norms for weight[e]	0.91 (0.61, 1.36)	1.19 (0.95, 1.49)	1.15 (0.91, 1.44)
Social norms for diet[e]	0.95 (0.65, 1.39)	1.04 (0.83, 1.32)	1.04 (0.82, 1.33)
Social norms for PA[e]	1.21 (0.80, 1.82)	0.93 (0.73, 1.20)	0.94 (0.72, 1.21)
WC efficacy expectancies[f]	0.94 (0.77, 1.14)	0.92 (0.83, 1.02)	0.94 (0.84, 1.05)
WC outcome expectancies[f]	1.01 (0.80, 1.28)	1.03 (0.91, 1.17)	**1.32 (1.13, 1.53)*****
Diet efficacy expectancies[f]	1.20 (0.99, 1.45)	1.00 (0.91, 1.09)	0.93 (0.85, 1.03)
Diet outcome expectancies[f]	1.00 (0.79, 1.26)	0.98 (0.86, 1.11)	1.13 (0.97, 1.32)
PA efficacy expectancies[f]	1.01 (0.84, 1.21)	**1.17 (1.06, 1.29)*****	**1.23 (1.11, 1.36)*****
PA outcome expectancies[f]	0.97 (0.85, 1.11)	**1.14 (1.05, 1.23)****	**1.23 (1.13, 1.34)*****
Nativity (US born)	1.05 (0.20, 5.45)	0.63 (0.26, 1.50)	0.58 (0.23, 1.41)

Notes: OR=odds ratio; CI=confidence interval; REF= reference category; BMI=body mass index;

PA=physical activity; WC=weight control. Results bolded when p≤0.05.

[a] Reference category was ‘believe a little’
[b] Reference category was ‘underweight or normal weight’.
[c] Reference category was ‘high school education or less’.
[d] Modeled as continuous with larger values representing greater causal beliefs (range: 1-4).
[e] Modeled as continuous with larger values representing greater social norms (range: 0-5).
[f] Modeled as continuous with larger values representing greater efficacy and outcome expectancies (range: 0-10).

* p≤0.05; ** p≤0.01; *** p≤0.001

Table S 3.2: Multinomial logistic regression model of genetic causal beliefs for obesity adjusted for demographic factors, psychosocial factors, and nativity (n=855).

Variable (REF)	Adjusted OR (95% CI)[a]		
	Don't believe at all	Believe quite a bit	Believe a lot
Ethnicity (Caucasian)	**2.49 (1.09, 5.70)***	0.83 (0.46, 1.51)	1.77 (0.77, 4.01)
Age (40 - ≤51)	**2.41(1.54, 3.78)*****	1.38 (0.97, 1.97)	**2.22 (1.31, 3.78)****
BMI[b]			
Overweight	0.59 (0.32, 1.11)	0.77 (0.47, 1.23)	0.60 (0.27, 1.34)
Obese or severely obese	0.69 (0.38, 1.26)	0.72 (0.45, 1.15)	0.95 (0.46, 1.95)
Education[c]			
Some college or associate degree	063 (0.34, 1.16)	1.09 (0.68, 1.76)	1.01 (0.50, 2.03)
Bachelor's or advanced degree	0.51 (0.26, 0.99)	0.90 (0.55, 1.49)	1.02 (0.49, 2.12)
Employment status (employed)	**0.59 (0.38, 0.93)***	**0.59 (0.41, 0.84)****	**0.49 (0.29, 0.84)****
Health insurance status (insured)	0.93 (0.54, 1.60)	1.12 (0.72, 1.74)	0.87 (0.46, 1.65)
Diet causal beliefs[d]	1.18 (0.87, 1.62)	1.09 (0.85, 1.40)	1.33 (0.89, 1.98)
PA causal beliefs[d]	0.85 (0.64, 1.12)	0.86 (0.67, 1.10)	1.10 (0.75, 1.61)
Social norms for weight[e]	1.05 (0.87, 1.26)	1.15 (0.98, 1.35)	**1.49 (1.18, 1.87)*****
Social norms for diet[e]	1.09 (0.89, 1.34)	1.03 (0.87, 1.22)	1.04 (0.81, 1.34)
Social norms for PA[e]	0.83 (0.67, 1.04)	0.95 (0.79, 1.15)	1.01 (0.77, 1.33)
WC efficacy expectancies[f]	1.10 (0.98, 1.22)	1.03 (0.95, 1.12)	0.93 (0.82, 1.05)
WC outcome expectancies[f]	1.06 (0.93, 1.21)	0.99 (0.89, 1.11)	1.07 (0.90, 1.28)
Diet efficacy expectancies[f]	0.99 (0.91, 1.08)	1.03 (0.97, 1.11)	1.00 (0.90, 1.11)
Diet outcome expectancies[f]	0.98 (0.85, 1.12)	1.01 (0.90, 1.13)	1.04 (0.93, 1.17)
PA efficacy expectancies[f]	0.94 (0.85, 1.03)	0.95 (0.87, 1.01)	1.06 (0.94, 1.20)
PA outcome expectancies[f]	**0.92 (0.85, 0.99)***	1.00 (0.92, 1.08)	**0.90 (0.82, 0.99)***
Nativity (US born)	**4.44 (1.99, 9.90)*****	1.44 (0.78, 2.67)	1.01 (0.42, 2.43)

Notes: OR=odds ratio; CI=confidence interval; REF= reference category; BMI=body mass index; PA=physical activity; WC=weight control. Results bolded when p≤0.05.

[a] Reference category was 'believe a little'
[b] Reference category was 'underweight or normal weight'.

[c] Reference category was ‘high school education or less’.
[d] Modeled as continuous with larger values representing greater causal beliefs (range: 1-4).
[e] Modeled as continuous with larger values representing greater social norms (range: 0-5).
[f] Modeled as continuous with larger values representing greater efficacy and outcome expectancies (range: 0-10).

* p≤0.05; ** p≤0.01; *** p≤0.001

Table S 3.3: Multinomial logistic regression model of genetic causal beliefs about obesity in Hispanic women adjusted for demographic, psychosocial, and acculturation factors (n=392).

Variable (REF)	Adjusted OR (95% CI)[a]		
	Don't believe at all	Believe quite a bit	Believe a lot
Age (40 - ≤51)	**2.86 (1.55, 5.28)****	**2.53 (1.28, 4.99)****	**2.96 (1.26, 6.98)***
BMI[b]			
Overweight	0.54 (0.21, 1.36)	0.43 (0.16, 1.11)	0.32 (0.09, 1.08)
Obese or severely obese	0.63 (0.25, 1.59)	**0.36 (0.14, 0.91)***	0.31 (0.10, 1.03)
Education[c]			
Some college or associate degree	0.98 (0.41, 2.33)	0.94 (0.39, 2.31)	1.21 (0.40, 3.67)
Bachelor's or advanced degree	0.36 (0.13, 1.01)	0.62 (0.24, 1.61)	0.63 (0.17, 2.31)
Employment status (employed)	0.61 (0.34, 1.10)	0.70 (0.37, 1.32)	0.49 (0.21, 1.11)
Health insurance status (insured)	1.10 (0.54, 2.21)	0.72 (0.34, 1.52)	1.18 (0.46, 3.05)
Diet causal beliefs[d]	1.17 (0.79, 1.74)	1.17 (0.75, 1.83)	1.26 (0.68, 2.35)
PA causal beliefs[d]	0.87 (0.62, 1.23)	0.86 (0.59, 1.26)	1.35 (0.78, 2.36)
Social norms for weight[e]	1.22 (0.96, 1.54)	**1.33 (1.02, 1.49)***	**1.61 (1.16, 2.24)****
Social norms for diet[e]	1.01 (0.78, 1.30)	0.85 (0.64, 1.13)	0.94 (0.65, 1.35)
Social norms for PA[e]	0.96 (0.73, 1.26)	1.15 (0.86, 1.55)	1.18 (0.81, 1.71)
WC efficacy expectancies[f]	1.12 (0.99, 1.26)	1.05 (0.91, 1.20)	1.04 (0.86, 1.26)
WC outcome expectancies[f]	0.95 (0.81, 1.12)	0.91 (0.75, 1.10)	1.04 (0.79, 1.39)
Diet efficacy expectancies[f]	1.07 (0.95, 1.21)	1.03 (0.90, 1.17)	1.05 (0.88, 1.26)
Diet outcome expectancies[f]	0.90 (0.75, 1.07)	1.03 (0.83, 1.27)	0.93 (0.69, 1.25)
PA efficacy expectancies[f]	0.90 (0.79, 1.01)	0.93 (0.81, 1.07)	0.91 (0.75, 1.09)
PA outcome expectancies[f]	0.95 (0.86, 1.03)	1.07 (0.96, 1.19)	0.99 (0.87, 1.13)
Nativity (US)	2.72 (0.56, 13.22)	2.76 (0.90, 8.47)	1.68 (0.35, 7.97)
Survey language (English)	3.19 (0.77, 13.11)	**0.22 (0.07, 0.68)****	0.76 (0.16, 3.53)

Notes: OR=odds ratio; CI=confidence interval; REF= reference category; BMI=body mass index; PA=physical activity; WC=weight control. Results bolded when p≤0.05.

[a] Reference category was 'believe a little'

[b] Reference category was ‘underweight or normal weight’.
[c] Reference category was ‘high school education or less’.
[d] Modeled as continuous with larger values representing greater causal beliefs (range: 1-4).
[e] Modeled as continuous with larger values representing greater social norms (range: 0-5).
[f] Modeled as continuous with larger values representing greater efficacy and outcome expectancies (range: 0-10).

* p≤0.05; ** p≤0.01; *** p≤0.001

-Chapter 4-

CAN SYSTEMATIC REFERRAL TO COUNSELING ADDRESS DISPARITIES IN GENETIC SERVICES UTILIZATION BY EDUCATION LEVEL? AN EXPLORATORY ANALYSIS

INTRODUCTION

Individuals with deleterious mutations in breast cancer susceptibility genes 1 and 2 (*BRCA 1/2),* have a 60-80% lifetime risk of breast cancer and a 10-45% lifetime risk of ovarian cancer, but can undergo enhanced screening regimens or prophylactic surgeries that dramatically reduce cancer risk.[1-3] Despite evidence of the clinical utility of *BRCA 1/2* testing and the existence of guidelines recommending referral to genetic counseling for high-risk women genetic services are under-utilized, largely due to physical under-referral.[4,5] Furthermore, factors other than medical need and patient preferences frequently drive utilization.[6] Education is a key sociodemographic characteristic predicting current utilization of genetic services. Women with fewer years of formal education are less likely to be appropriately referred to genetic counseling and undergo genetic testing, even when insurance coverage is not a barrier.[4,7,8] This pattern is indicative of health care disparities, i.e. inequities in access to and quality of genetic services by education level.[9,10]

Researchers have proposed systematically identifying and referring high-risk patients to genetic counseling as a strategy to combat physician under-referral and increase use of both genetic services and risk-appropriate preventive strategies.[11] This approach may also decrease disparities in utilization of genetic services by standardizing the referral process and providing equitable access to genetic counseling for all women, regardless of their education level.[12] Genetic counseling enables individuals to make testing and risk-management decisions that are based on relevant knowledge, consistent with their values, and behaviorally implemented by providing comprehensive risk assessment, education about the benefits and limitations of genetic testing, and psychosocial support.[13] Examining whether uptake of genetic counseling and subsequent informed decision-making differs by education level is important for determining how routine referral will impact disparities in the utilization of genetic services and cancer preventive interventions.

Education level may moderate systematic referral to genetic counseling's effects in a number of ways. Uptake of counseling and follow-through on risk reduction recommendations could vary due to differences in the self-management skills and personal agency involved in successfully managing health complex health problems. These skills are developed, in part, though formal education.[14] Additionally, counseling may inconsistently facilitate informed decision-making if less educated women have trouble translating objective risk estimates into accurate cancer risk perceptions and test candidacy judgments, important knowledge-related targets of genetic counseling.[15,16] Prior research indicates that even highly education individuals have trouble interpreting the type of probabilistic information presented during genetic counseling sessions.[17] Alternatively, less educated women could derive greater benefit from counseling, as sessions provide individually tailored education and one-on-one psychosocial support. Theorists have proposed that this type of health communication may lead to larger gains in knowledge and agency in individuals with limited health literacy.[18] Supporting this point, a prior randomized controlled trial (RCT) indicated that personalized counseling led to greater reductions in breast-cancer-specific distress for those with less than a high school education.[19]

This exploratory study investigates the above hypotheses about systematic referral to genetic counseling in high-risk women with and without a college degree. Specifically, we examine systematic referral's effect on participation in genetic counseling; changes in cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments; and likelihood of undergoing genetic testing and test for effect-modification by education level.

METHODS

Participants and procedures

Data for this study come from a randomized control trial (RCT) designed to assess systematic referral to genetic counseling's effect on uptake of risk-reducing salpingo-oophorectomy (RRSO)—surgical removal of the ovaries and Fallopian tubes. Main analyses indicated that systematic referral was associated with a

3-fold increase in the two-year incidence of RRSO (hazards ratio: 3.44; 95% CI: 0.95, 12.49).[11] The RCT procedures were as follows:

All women ages 35-80 who received a mammogram between January 2006 and April 2008 at three mammography facilitates in Seattle, Washington and also had a family history of breast cancer and no prior ovarian cancer diagnosis or RRSO indicated in their electronic medical record were informed of the study and mailed a detailed screening questionnaire. A total of 12,919 screening questionnaires were mailed: 552 were undeliverable and 2,797 were completed and returned. Based on the personal and family cancer history information provided at screening, a total of 1,114 women met initial eligibility criteria and were mailed a baseline questionnaire to gather additional information about their reproductive history, cancer history, and lifestyle factors. A total of 489 women did not return the baseline questionnaire or were otherwise excluded at this stage, leaving 625 eligible high-risk women who were invited to participate in the RCT. Of these, 167 either declined or did not respond to enrollment scheduling attempts. The remaining 458 women attended a study enrollment appointment and were randomized to either be referred to free genetic counseling (intervention arm, n=228) or received standard of care as defined by their primary care provider (control arm, n=230). Eligible women who enrolled in the RCT had a higher rate of Ashkenazi Jewish ancestry and regular mammography use, but were otherwise similar to those who declined participation in terms of demographics, cancer worry, and cancer history. Women randomized into the intervention and control arms were similar except for a slight difference in their age distributions.

Genetic counseling sessions for women in the intervention arm were conducted by a certified genetic counselor and followed standard practices. Women were encouraged to schedule an appointment with the study's genetic counselor at enrollment. Those who had not scheduled an appointment after three weeks received one follow-up reminder letter. Participants in both arms received mailed follow-up questionnaires at 12 and 24 months following enrollment that assessed use of genetic services, cancer risk-reduction practices, ovarian cancer knowledge, and psychosocial outcomes. Follow-up questionnaires were returned by 225 (98%) and 215 (94%) of the women in the standard care and

intervention arms, respectively. Women in the intervention arm who attended genetic counseling also completed a questionnaire shortly following their appointment.

Measures

Measures of interest in this study (cancer relative risk perceptions, testing awareness, and test candidacy judgments) were self-reported in the screening and follow-up questionnaires. Relative risk perceptions and test candidacy judgments were also measured in the post-counseling questionnaire. These measures were selected based on models of informed decision-making for genetic counseling and their use in prior studies.[13,16,20,21] Breast and ovarian cancer relative risk perceptions were assessed separately by asking women to indicate if they felt their chance of getting each cancer was "much lower", "a little lower", "about the same", "a little higher", or "much higher" compared to other women their age. To measure genetic testing awareness women were asked how much they had read or heard about genetic testing. Response options included "almost nothing", "relatively little", "a fair bit", and "a lot". Women also indicated if they thought that they would be an appropriate candidate for genetic testing given their family history as "definitely not", "probably not", "probably yes", or "definitely yes", which was used as a measure of test candidacy judgments. Based on their responses women were classified (yes or no) as believing their chance of getting breast and ovarian cancer was higher than other women their age, as having read or heard at least a fair bit about genetic testing, and as correctly identifying as an appropriate candidate for genetic testing given their family history.

Genetic counseling attendance and genetic testing utilization during the study period was self-reported in the follow-up questionnaires. For women in the intervention arm self-reports were supplemented using study records. Women were classified as at least college graduates (yes or no) based on their highest level of formal education reported at baseline. Other variables self-reported prior to enrollment included: age, race/ethnicity, prior genetic testing, *BRCA* mutation status, prior breast cancer diagnoses, and breast and ovarian cancer diagnoses among first and second degree relatives.

Statistical analysis

Descriptive statistics were used to characterize women assigned to each arm at enrollment. Differences in breast cancer relative risk perceptions, ovarian cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments at screening by education level were examined using Pearson's chi-squared test. Differences in uptake of counseling after referral by patient demographics and cancer history were examined using Fisher's exact test in the intervention arm.

The effect of referral to genetic counseling on changes in breast cancer relative risk perceptions, ovarian cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments between screening and 12- and 24-month follow-up were estimated in separate logistic regression models. Generalized estimating equations with independent working correlations and robust standard errors were used to account for the correlation of women's responses over time. Differential effects of referral to counseling by education level were examined by adding a three-factor interaction between time, group assignment, and education level to each model. Logistic regression was also used to estimate the effect of offering genetic counseling on the likelihood of undergoing genetic counseling and testing during the study. Differential effects by education level were examined using a two-way interaction between group assignment and education level.

To aid in interpretation of the logistic regression results, post-estimation techniques were employed to translate the log-odds of outcomes of interest into predicted probabilities across groups of women defined by education level and/or study arm.[22] Logistic regression models used complete cases and statistical testing was performed using Wald tests and considered significant at $p \leq 0.05$. Secondary analyses excluding women who had undergone genetic testing at enrollment and exploring short-term changes in cancer risk perceptions and test candidacy judgments in women who participated in free genetic counseling were also conducted. All analyses were performed in 2015 using Stata 13 software (StataCorp, 2013).

Ethics

Ethical approval of all study procedures was obtained from the Fred Hutchinson Cancer Research Center Institutional Review Board. In the study's introductory letter women were told that they had been identified based on their past mammography participation and that they might be offered the opportunity to take part in cancer prevention research based on their responses to the enclosed screening questionnaire. All study participants provided written informed consent.

RESULTS

Descriptive characteristics

Study participants characteristics are provided in Table 4.1. Participants were mainly between the ages of 45 and 65, White, and had at least a college degree. Approximately 15% identified as Ashkenazi Jewish, 30% had previously been diagnosed with breast cancer, and 88% and 21%, respectively, had one or more relative with breast or ovarian cancer. About 15% report prior genetic testing, with two women in each arm having known *BRCA* mutations at enrollment.

Table 4.2 describes cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments at screening in women with and without a college degree. Only ovarian cancer relative risk perceptions differed by education level; 34% of women without a college degree believed that their chance of getting ovarian cancer was higher than other women their age, compared with 29% of college graduates ($p \leq 0.05$). At screening, 73% of women believed their chance of getting breast cancer was higher than other women their age, 47% reported having read or heard at least a fair bit about genetic testing, and 75% correctly identified as an appropriate candidate for genetic testing given their family history.

Systematic referral's effect on participation in genetic counseling

Counseling uptake after referral was 85% based on study records—197 of the 228 women in the intervention arm offered free genetic counseling attended a session. Participation in counseling did not differ by education level ($p \leq 0.36$). Compared with those who attended counseling, women who did not

more often had previously received genetic testing (11% vs. 29%), reported having read or heard at least a fair bit about genetic testing (43% vs. 68%), and had three or more female relatives with breast cancer (18% vs. 29%). Additionally, three of the four Hispanic participants referred to counseling did not participate as well as both women who reported a *BRCA* mutation at study enrollment. Women in the intervention arm had a 78% higher probability of attending genetic counseling during the study than those receiving standard of care (95% CI: 0.72, 0.83; p≤0.01). This effect did not differ by education level.

Systematic referral's effect on changes in cancer risk perceptions, genetic testing awareness, test candidacy judgments, and subsequent testing

Missing data for the outcome measures of interest ranged from zero to 17% (for ovarian cancer relative risk perceptions at 24 month follow-up) and did not differ by education level. Table 4.3 provides referral's effect on changes in cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments between screening and follow-up. Referral to free genetic counseling had no effect on breast or ovarian cancer relative risk perceptions or on women's assessments of whether they were appropriate candidates for testing—these outcomes did not significantly differ between screening and follow-up in either the intervention or control arms. Systematic referral did change women's probability of reporting to have read or heard at least a bit about genetic testing. At 12 month follow-up, women referred to genetic counseling had a 20% (95% CI: 0.10, 0.31; p≤0.01) greater increase in their probability of endorsing this outcome compared to women who received standard of care. At 24 month the difference between arms fell to 14% (95% CI: 0.03, 0.24; p≤0.01). There was no evidence of differential intervention effects on cancer relative risk perceptions or genetic testing awareness by education level; none of the interactions reached statistical significance.

Figure 4.1 indicates the predict probability of undergoing genetic testing during the study by group assignment and education level. Referral to free genetic counseling significantly increased the likelihood of undergoing testing and this effect did not differ by education level. Women in the intervention arm had a 23% higher probability of getting testing during the study than those receiving standard of care (95% CI: 0.16, 0.30, p≤0.01). Excluding women with prior genetic testing at enrollment did not qualitatively change

these findings, though effect sizes for attending genetic counseling, reporting to have read or heard at least a bit about genetic testing, and undergoing genetic testing during the study all increased slightly.

Short-term changes risk perceptions and candidacy judgments in the intervention arm

The secondary analysis of short-term changes in cancer risk perceptions and test candidacy judgments in women who participated in free genetic counseling showed statistically significant increases in ovarian cancer relative risk perceptions and test candidacy judgments from screening to directly following genetic counseling. Post-counseling, 65% of women believed their chance of getting ovarian cancer was higher than other women their age (vs. 35% at screening) and 89% correctly identified as an appropriate candidate for genetic testing (vs. 77% at screening). Ovarian cancer relative risk perceptions and test candidacy judgments had returned to screening levels by 12 month follow-up. Breast cancer relative risk perceptions did not change over the course of the study.

Only ovarian cancer relative risk perceptions showed evidence of differential changes over time by education level (illustrated in Figure 4.2). Women with at least a college education had a 35% (95% CI: 0.26, 0.45; $p \leq 0.001$) increase in their probability of believing that their chance of getting ovarian cancer was high compared with other women their age from screening to directly following counseling. Ovarian cancer relative risk perceptions did not change significantly for women without a college degree (Difference: 0.11; 95% CI: -0.10, 0.33; $p \leq 0.03$). This eliminated baseline differences in relative risk perceptions by education, which remained negligible at 12 and 24 month follow-up. Changes in women's probability of believing that their chance of getting ovarian cancer was high compared with others their age between screening and 12 and 24-month follow-up were consistently negative for those without a college degree and consistently positive for those who had at least graduated college—leading to statistically significant interaction effects at both time points ($p \leq 0.04$ at 12 months & $p \leq 0.03$ at 24 months).

DISCUSSION

Results from this exploratory study indicate that systematically identifying and referring high-risk women to genetic counseling using electronic medical records and mailed questionnaires has largely similar

effects for women with and without a college degree. Specifically, uptake of counseling did not differ by education, nor did the intervention's effect on changes in genetic testing awareness and likelihood of subsequent genetic testing during the study, which increased for all women. Secondary analyses did suggest that increases in ovarian cancer relative risk perceptions that briefly following participation in genetic counseling are greater for women with at least a college degree, effectively equalizing differences by education that exist at screening.

These findings must be contextualized with respect to our prior hypotheses about how referral's effects may differ by education. First, women without a college degree were not less likely to follow through on referrals to free genetic counseling, as proposed. Other factors, including prior use of genetic services and prior awareness of genetic testing, primarily influenced uptake of genetic counseling. This suggest that referring high risk women to genetic counseling and sending them a single reminder letter to make an appointment may be enough to allow most women who want to participate in counseling to follow-through on their intentions, regardless of their education level. Our finding that the likelihood of undergoing genetic testing after counseling did not differ by education also indicates that once women are funneled into counseling, existing systems for navigating them through downstream health care actions may be sufficient at overcoming differences in personal agency and self-management skills. This is a tentative hypothesis that warrants future study, particularly by examining variation in more complex health care actions such as adherence to enhanced screening regimens by education level.

Second, we hypothesized that the genetic counseling could have different effects on outcomes important to informed decision-making, included cancer risk perceptions, genetic testing awareness, and test candidacy judgments for women with and without a college degree. Our results indicate that genetic counseling had minimal effects on most of these outcomes, regardless of education level. Specifically there were no changes in women's breast cancer risk perceptions. Short term increases in test candidacy judgments from screening to directly following counseling were unlikely to be clinically significant and did not differ by education. These findings could be due to the fact that at screening the majority of women, both with and without college degrees, already recognized they were at higher risk for breast cancer than

other women their age (73%) and that they were appropriate candidates for genetic testing, given their family history (75%). These observations suggest increasing public recognition of the family health history that makes someone a candidate for BRCA 1/2 testing, which does not align with the low levels of genetic testing awareness we observed at baseline (47% of women reporting having read or heard at least a bit about genetic testing). One possible explanation for this discrepancy is that women may have interpreted our measure of testing awareness as reflecting the extent to which they had actively sought out information on genetic testing, while their prior exposure to this information may have been more passive (e.g. through mass media).

The results for ovarian cancer relative risk perceptions are more difficult to interpret. Women with at least a college education who participated in genetic counseling had significantly larger short-term increases in relative risk perceptions compared with those without a college degree. From a health literacy perspective, where ideally all women would recognize their high relative risk of ovarian cancer following genetic counseling, this could be seen as indicated that low education women did not equally benefit from genetic counseling, perhaps due to difficulties interpreting the risk information they were provided.[15,17] A number of clinical and psychosocial factors in addition to objective risk shape cancer risk perceptions.[23] The differences in ovarian cancer relative risk perceptions by education we observed at baseline could therefore reflect factors other than recognition objective risk. To this point, less educated women had higher levels of worry about their ovarian cancer risk at baseline, but not following genetic counseling. This could indicate that participating in genetic counseling helped address ovarian cancer worry in women without a college degree, while continuing to convey their elevated risk status. This interpretation aligns more closely with our hypothesis that low education women have more to gain from the type of personalized support and education provided through genetic counseling.[18,19] Future qualitative work could help clarify how women with different degrees of formal education understand their ovarian cancer risk before and after genetic counseling and the implications this has for their health behaviors.

The study had a number of limitations. The sample is highly educated, lowering our power to test interaction terms in subgroup analyses. Furthermore, differences in our outcomes of interest between

women with and without a college degree are likely less meaningful than differences between those who did and did not graduate from high school. We also have no information about financial resources, a key predictor of genetic services utilization, though genetic counseling was free and the study's randomized design helps to minimize this concern.[24] Self-reports of counseling and testing utilization were supplemented with study records for women in the intervention arm, but not for women receiving standard of care. Receipt of counseling and testing was under-reported in the intervention arm. If this pattern holds in the control arm our estimated effect sizes for referral's impact on participating in genetic counseling and testing are likely inflated. Finally, we have no information about women who did not respond to the screening and baseline questionnaires, making it difficult to draw conclusions about the broader generalizability of our finding. It is clear that our results primarily apply to insured, White, well-educated women participating in screen mammography, who are less likely to experience health care disparities.

Conclusion

Despite these limitations, this study provides important preliminary data about the effects of systematic referral to genetic counseling for women with and without a college education. Education is a plausible *a priori* effect modifier chosen based on prior research, not exploration of RCT data. Though our findings should be confirmed in more representative samples, this exploratory study suggests that interventions that routinely refer high-risk women to genetic counseling may help reduce disparities in utilization of genetic services, in addition to increasing overall use of genetic counseling, genetic testing, and surgical prevention.[11] If these findings prove to be broadly generalizable, widespread dissemination of intervention involving systematic referral may lead to more equitable genetic services delivery and improve cancer-related outcomes for high-risk women.

REFERENCES

1. Antoniou A, Pharoah PDP, Narod, S., et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003;72:117-30.

2. Rebbeck TR, Lynch HT, Neuhausen Sal, et al. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. *N Engl J Med.* 2002;346:1616-22.

3. Rebbeck TR, Levin AM, Eisen A, et al., Breast cancer risk after bilateral prophylactic oophorectomy in *BRCA1* mutation carriers. *J Natl Cancer Inst.* 1999;91:1475-9.

4. Bellcross CA, Peipins LA, McCarty FA, et al. Characteristics associated with genetic counseling referral and BRCA 1/2 testing among women in a large integrated health system. *Gen in Med.* 2014; 17:43-50.

5. Levy DE, Byfield SD, Comstock CB, et al. Underutilization of BRCA 1/2 testing to guide breast cancer treatment: black and Hispanic women particularly at risk. *Genet Med.* 2011;13:349-55.

6. Hall M, Olopade OI. Confronting genetic testing disparities: knowledge is power. *JAMA.* 2005;293:1783-5.

7. Bellcross CA, Leadbetter SD, Alford SH, Peipins LA. Prevalence and healthcare actions of women in a large health system with a family history meeting the 2005 USPSTF recommendations for BRCA genetic counseling referral. *Cancer Epidemiol Biomarkers Prev.* 2013; 22:728-35.

8. Olaya W, Esquivel P, Wong JH, et al. Disparities in BRCA testing: when insurance coverage is not a barrier. *Am J Surg.* 2009;198:562-5.

9. Kaiser Family Foundation. *Disparities in Health and Health Care: Five Key Questions and Answers.* 2012. Menlo Park, CA: KFF. http://kff.org/disparities-policy/issue-brief/disparities-in-health-and-health-care-five-key-questions-and-answers/. Published 2012. Accessed August 1, 2015.

10. Anderson RM, Newman JF. Societal and individual determinants of medical care utilization in the United States. *Milbank Memorial Fund Quarterly- Health and Society.* 1973;51:95-124.

11. Drescher CW, Beatty JD, Resta R, et al. Effect of referral for genetic counseling on surgical prevention in women at high risk for ovarian cancer. Manuscript submitted for publication.

12. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines: a framework for improvement. *JAMA.* 1999;282:1458-65.

13. Berliner JL, Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2007; 16:241-60.

14. Mirowsky J, Ross CE. Education, Social Status and Health. New York: Aldine De Gruyter, 2003.

15. Hurle B, Citrin T, Jenkins JF, et al. What does it mean to be genomically literate?: National Human Genome Research Institute Meeting Report. *Gent Med.* 2013;15:658-63.

16. Biesecker BB. Goals of genetic counseling. *Clin Genet.* 2001;60:323-330.

17. Lea DH, Kaphingst KA, Bowen D, Lipkus I, Hadley DW. Communicating genetic and genomic information: health literacy and numeracy considerations. *Public Health Genomics.* 2011;14:279-89.

18. Nutbeam D. The evolving concept of health literacy. *Soc Sci Med.* 2008;67:2072-8.

19. Lerman C, Schwartz MD, Miller SM, Daly M, Sands C, Rimer BK. A randomized trial of breast cancer risk counseling: interacting effects of counseling, education level, and coping style. *Health Psychol*. 1996;15:75-83.

20. Andersen MR, Nelson J, Peacock S, et al. Worry about cancer risk and use of screening by high risk women: how you recruit affects what you find. *Am J Med Genet A.* 2004;129:130-5.

21. Andersen MR, Bowen D, Yasui Y, McTiernan A. Awareness and concern about ovarian cancer among women at risk because of a family history of breast or ovarian cancer. *Am J Obstet Gynecol*. 2003;189:S42-7.

22. Williams, R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. *Stata Journal*. 2012;12:308-331.

23. Tilburt JC, James KM, Sinicrope PS, Eton DT, Costello BA, Carey J, Lane MA, Ehlers SL, Erwin PJ, Nowakowski KE, Murad MH. Factors influencing cancer risk perception in high risk populations: a systematic review. *Hered Cancer Clin Pract.* 2011;9:2.

24. Kieran S, Loescher LJ, Lim KH. The role of financial factors in acceptance of clinical *BRCA* genetic testing. *Genet Test.* 2007;11:101-10.

TABLES

Table 4.1: Enrollment characteristics by study arm.

Variable	Response category	Control arm	Intervention arm
N (%)		230 (50.2%)	228 (49.8%)
Age in years	35 ≤ age ≤ 44	43 (18.7%)	43 (18.9%)
	45 ≤ age ≤ 54	109 (47.4%)	86 (37.7%)
	55 ≤ age ≤ 64	47 (20.4%)	72 (31.6%)
	65 ≤ age ≤ 90	31 (13.5%)	27 (11.8%)
	Missing	0 (0%)	0 (0%)
	[Mean ± SD]	[53 ± 10]	[54 ± 10]
Race/ethnicity[a]	Non-White race	17 (14.9%)	21 (9.2%)
	Hispanic ethnicity	4 (1.7%)	4 (1.75%)
	Missing	0 (0.0%)	0 (0.0%)
Ashkenazi Jewish	Yes	36 (15.7%)	34 (14.9%)
	Missing	37 (16.1%)	41 (18.0%)
Education	College graduate or beyond	178 (77.4%)	177 (77.6%)
	Missing	2 (0.9%)	4 (1.8%)
No. of relatives with ovarian cancer[b]	1	42 (18.3%)	37 (16.2%)
	2	7 (3.0%)	5 (2.2%)
	3+	1 (0.9%)	2 (0.9%)
	Missing	0 (0%)	0 (0%)
No. of female relatives with breast cancer[b]	1	98 (42.6%)	96 (42.1%)
	2	60 (26.1%)	59 (25.9%)
	3+	44 (19.1%)	44 (19.3%)
	Missing	0 (0%)	0 (0%)
Personal cancer history	Had breast cancer	65 (28.3%)	71 (31.1%)
	Missing	0 (0%)	0 (0%)
Prior genetic testing	Yes	37 (16.1%)	31 (13.6%)
	Missing	1 (0.4%)	2 (0.9%)
BRCA status	BRCA 1 or 2 mutation	2 (0.9%)	2 (0.9%)
	Missing	0 (0%)	0 (0%)

[a] Race and ethnicity not mutually exclusive.
[b] Counts include first and second degree relatives.

Table 4.2: Cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments at screening, by education level.

		Less than college degree, n (%)	At least a college degree, n (%)	*p*-value[a]
		n=97	n=355	
Chances of getting breast cancer compared to women my age are:	Higher	75 (77.3%)	252 (71.0%)	0.229
	Missing	1 (1.0%)	5 (1.4%)	
Chances of getting ovarian cancer compared to women my age are:	Higher	33 (34.0%)	102 (28.7%)	0.049
	Missing	18 (18.6%)	18 (5.1%)	
How much have you read or heard about genetic testing?	At least a fair bit	47 (48.5%)	164 (46.2%)	0.710
	Missing	0 (0%)	1 (0.3%)	
Appropriate candidate for genetic testing given family history:	Yes	76 (78.4%)	263 (74.1%)	0.248
	Missing	3 (3.1%)	5 (1.4%)	

[a] From Pearson's chi-squared test, excluding missing data.

Table 4.3: Effect of systematic referral to genetic counseling on changes in changes in cancer relative risk perceptions, genetic testing awareness, and test candidacy judgments from screening to follow-up.

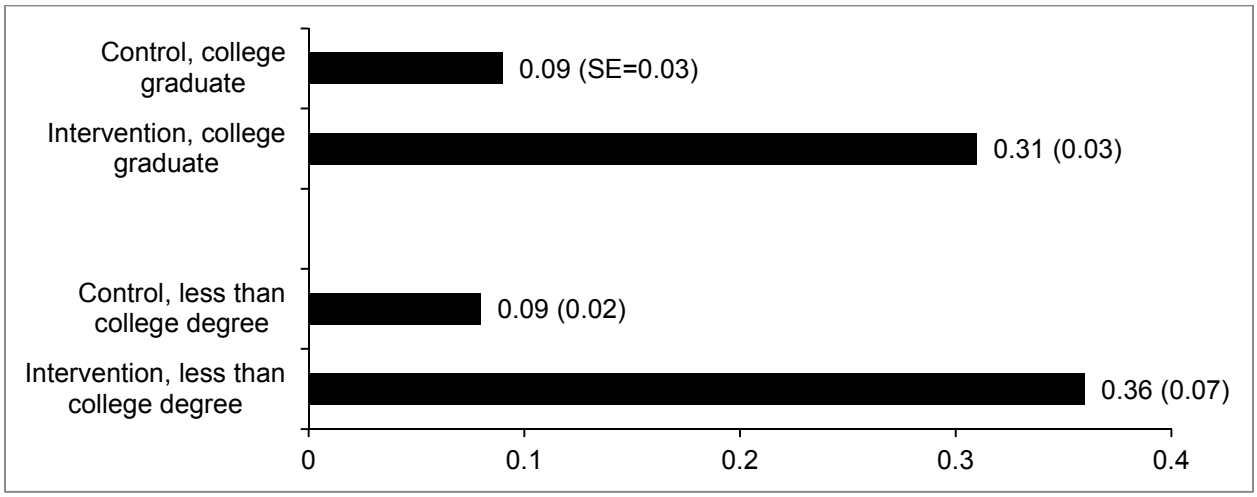
	At 12 month follow-up			At 24 month follow-up		
	Change in Intervention Arm (95% CI)	Change in Control Arm (95% CI)	Difference in Changes (95% CI)	Change in Intervention Arm (95% CI)	Change in Control Arm (95% CI)	Difference in Changes (95% CI)
Predicted probability of believing chance of getting breast cancer is high compared to women her age (n=458)	-0.01 (-0.07, 0.04)	0.03 (-0.02, 0.09)	-0.04 (-0.12, 0.04)	-0.05 (-0.11, 0.02)	-0.04 (-0.09, 0.02)	-0.01 (-0.10, 0.07)
Predicted probability of believing chance of getting ovarian cancer is high compared to women her age (n=452)	0.04 (-0.03, 0.11)	0.04 (-0.3, 0.10)	0.00 (-0.09, 0.10)	0.01 (-0.06, 0.04)	0.04 (-0.02, 0.011)	-0.03 (-0.13)
Predicted probability of reporting to have read and heard at least a fair bit about genetic testing (n=458)	**0.22 (0.14, 0.30)*** **	0.02 (-0.05, 0.08)	**0.20 (0.10, 0.31)*** **	**0.22 (0.13, 0.30)*** **	**0.08 (0.01, 0.04)***	**0.14 (0.03, 0.24)** **
Predicted probability of correctly identifying as an appropriate candidate for genetic testing given family history (n=458)	-0.01 (-0.8, 0.05)	-0.01 (-0.06, 0.05)	0.00 (-0.09, 0.08)	-0.02 (-0.9, 0.05)	0.02 (-0.04, 0.08)	-0.04 (-0.14, 0.05)

Notes: CI=confidence interval. Estimates bolded when p≤0.05.

*p≤0.05; **p≤0.01; ***p≤0.001

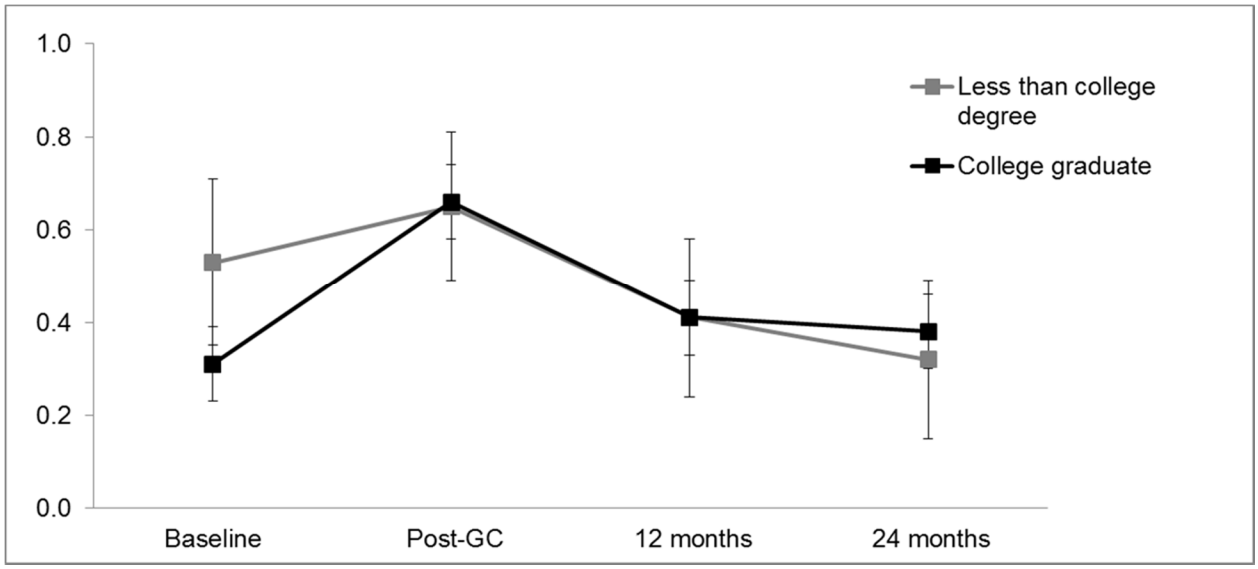
FIGURES

Figure 4.1: Predicted probability of undergoing genetic testing, by education and study arm (n=452).



Notes: SE=standard error.

Figure 4.2: Predicted probability of high perceived ovarian cancer relative risk in women in the intervention arm who participated in genetic counseling, by education level (n=191).



Notes: GC=genetic counseling

-Chapter 5-

CONCLUSION

Genomic health applications are poised to play a central role in precision medicine, a tailored approach to disease prevention and treatment that accounts for individual variability in genes, environments, and lifestyles.[1,2] Precision medicine is hypothesized to improve both individual and population health outcomes by personalizing health care and public health interventions.[3] Prior examples of intervention approaches that improved individual health, but widened outcome gaps for disadvantaged groups suggest that translating public investments in precision medicine into population health benefits requires deliberate attention to health equity.[4,5] Motivated by a normative model of the translational research cycle developed to help achieve population health-level impacts (Figure 1.1) this dissertation investigated how sociocultural factors shape the discovery, development, delivery, and health impact of genomic applications and the resulting implications for health disparities.[6]

The first study focused on the discovery phase, developing a six-item instrument measuring conflation of observational biospecimen-based research and clinical care for use in Latino communities, who are currently under-represented in genomic research studies.[7] This study utilized traditional psychometric scale-development procedures, including exploratory factor analysis.[8] The final instrument demonstrated high internal consistency, evidence of content and construct validity, and no evidence of floor and ceiling effects in a convenience sample of 150 Latino adults recruited in the Lower Yakima Valley in Washington State. We observed that Latinos who were unemployed, spoke only Spanish, had no health insurance, and received health care outside of traditional venues had higher scores, indicating a greater degree of conflation. We also found that individuals who reported providing a biological sample for research in the past tended to have lower scores than those who had not, tentatively suggesting that the recruitment and informed consent process may help clarify misconceptions about observational biospecimen-based research.

The second study focused on the development and delivery of obesity prevention and control interventions that include messages about inherited and behavioral risk factors. Specifically, it described variation in beliefs about the causes of obesity (inheritance, diet, and physical activity) between Hispanic and Caucasian women enrolled in a cohort study in South King County, Washington. It also investigated acculturation's role in shaping obesity attributions in Hispanic women. We calculated marginal effect estimates from multinomial logistic regression models to illustrate differences in obesity attributions between hypothetical populations of women defined by ethnicity and indicators of acculturation. Results showed that Hispanic and Caucasian women held different beliefs about inheritance and physical activity's contribution to obesity; ethnic differences in genetic attributions were more pronounced than differences in physical activity attributions. The substantial difference in genetic attributions by indicators of acculturation was the study's most novel finding: Hispanic women who completed the study's baseline questionnaire in Spanish vs. English had a 36% higher probability of not believing at all in inheritance as a contributor to obesity (95% CI: 0.26, 0.43; $p \leq 0.001$).

The third study focused on the delivery and health impact of genetic counseling and testing for hereditary breast and ovarian cancer—genomic health applications that are the current standard of care for high risk women.[9] Using secondary analysis of a randomized controlled trial conducted in Seattle, Washington we examined whether routine referral to genetic counseling using electronic medical record data and mailed questionnaires could help address existing disparities in utilization by education level.[10] Results indicated that uptake of counseling did not differ by education, nor did the intervention's effect on changes in genetic testing awareness and likelihood of subsequent genetic testing during the study, which increased for all women. Secondary analyses also showed that increases in ovarian cancer relative risk perceptions that briefly followed participation in genetic counseling were greater for women with at least a college degree, effectively equalizing differences by education that existed at screening.

Each of the three studies has its own limitations, as described in prior chapters. Of particular note, study one examined beliefs about biospecimen-based research in a community sample, not in prior biospecimen donors. Study two used a cross-sectional design, which enabled us to describe variation in

obesity attributions by ethnicity and acculturation indicators, but provided limited information about the causes or consequences of observed differences. Finally, study three was conducted in a well-educated sample, limiting our power to examine differential effects by education level. The dissertation as a whole has limitations that also warrant mention. First, the topics covered in each study as well as the specific sociocultural factors of interest were inconsistent, making it difficult to draw over-arching, actionable conclusions from our results. Using a health-equity impact assessment approach to examine the relative efficacy and effectiveness of a single genomic health application for a specific sociocultural group at each stage of translation would have enabled us to make more specific recommendations about how to prevent intervention-generated inequalities—at least in that specific scenario.[11] Second, each study was conducted in a targeted geographic area within Washington State. This limits the dissertation's generalizability to other regions, particularly outside of the United States. Finally, we did not explicitly consider issues of cost or cost-effectiveness. By focusing primarily on generalizability, efficacy, and effectiveness, we ignored the substantial role that efficiency (the extent to which a health intervention achieves its goal while minimizing resource usage) and other economic concerns play in shaping genomic translation.[5]

Many of the limitations mentioned above can also be re-framed as strengths. Specifically, the variability in topics and sociocultural characteristics of interest between studies has some advantages. Numerous interacting sociocultural factors place individuals at risk for experiencing health disparities, including place of residence, race, ethnicity, culture, language, occupation, gender/sex, religion, education, socioeconomic status, and social capital.[12] This dissertation explored health equity implications by ethnicity, indicators of acculturation, including language, and education level. Thus, the results provide an idea of the range of sociocultural factors that will impact genomic translation and illustrate the need to consider all of these characteristics, their interactions, and how they are embodied within individuals.[12] Second, our research questions spanned the full spectrum of genomic translation, from discovery to outcomes phases. The studies' results were therefore complementary while also providing novel insights at each phase that may have broader applications to other types of genomic interventions and/or disadvantaged subpopulations. Finally, the dissertation serves as an exemplar of how normative models

of research translation can be used to conduct ethics-oriented, multidisciplinary research. Prioritizing this type of scholarship—i.e. asking questions about equity instead of or in addition to questions about effectiveness and efficiency—will be necessary to make good on public investments in precision medicine.[6]

The larger implications and key take-away messages from this work are three-fold. First, standardization, systemization, and other approaches to decreasing inappropriate variation in access to genomic research participation opportunities and genomic health applications in the community are a promising way to minimize disparities. This finding reflects an often overlooked characteristic of health interventions: reliance on voluntary behavior change often leads to inequalities as not all health-related choices are unconstrained and preferences also shape intervention uptake and compliance.[5,13,14] As illustrated in study three, the more that can be done to minimize the effects of individual behavior (both patients' and providers') the greater the possible population health benefits. Second, intervention tailoring will be essential to avoiding inequalities. As shown in study two, genomic health applications that are delivered in the same way to all individuals are likely to lead to differential outcomes. Tough precision medicine is described as a personalized approach to health—the converse of current "one-size-fits-all" approaches—if disadvantaged groups are less able to access, understand, engage with, or comply with precision medicine interventions, public expectations of improved health will likely not be met. Thus, precision medicine interventions may need to be further tailored and targeted with a specific eye towards health equity.

Finally, each of the three studies revealed additional normative concerns and ethical implications beyond genomic translation's potential to widen health disparities. For example, study one raised the possibility that medically underserved populations may be participating in observational biospecimen-based research as a way to access otherwise unavailable health services, conflicting with expectations of informed consent and voluntary participation.[15] Study two also highlighted differences in beliefs about genomic causation by acculturation that may have larger ramifications for genetic determinism, stigma, racial essentialism, and stereotyping in the context of obesity.[16,17] Finally, study three indicated that low

education women at high-risk of hereditary breast and ovarian cancer are more worried about their cancer risk, raising the possibility of other negative psychosocial effects including anxiety, denial, low self-esteem, or guilt.[18] All of these observations represent important avenues for future research to help minimize harms, in addition to focusing on health status outcomes.

In conclusion, this dissertation provides a better understanding of how sociocultural factors shape the discovery, development, delivery, and health impact of genomic interventions. Trade-offs between effectiveness, efficiency, and equity goals are necessary to prevent intervention-generated inequalities and ensure that precision medicine approaches lead to population health benefits.[5] These three studies illustrate that normative models of research translation can help frame research studies that generate evidence to inform these choices.[6] Dedicated attention to health disparities is an essential component of large public investments in personalized approaches to disease prevention and treatment.[4,19]

REFERENCES

1. Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature.* 2011;470:204-13.

2. National Research Council. *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. Washington, DC: Nation Academies Press, 2011.

3. Collins FS, Varmus, H. A new initiative on precision medicine. *N Engl J Med.* 2015;372:793-5.

4. Kankwa-Mullan I, Bull J, Sy F. Precision medicine and health disparities: an advancing science of individualizing patient care. Am J Public Health. 2015;105:S368.

5. White M, Adams J, Heywood P. How and why do interventions that increase health overall widen inequalities within populations? In *Social Inequality and Public Health*. 2009. Bristol, UK: The Policy Press.

6. Kelley M, Edwards K, Starks H, et al. Values in translation: how asking the right questions can move translational science towards greater health impact. *Clin Trans Sci.* 2013;5:445-51.

7. Bustamante CD, Burchard EG, De La Vega FM. Genomics for the world. *Nature.* 2011;475:163-165.

8. Comfry AL. Factor-analytic methods of scale development in personality and clinical psychology. J *Consult Clin Psychol*. 1988;56:754-761.

9. Levy DE, Byfield SD, Comstock CB, et al. Underutilization of BRCA 1/2 testing to guide breast cancer treatment: black and Hispanic women particularly at risk. *Genet Med.* 2011;13:349-55.

10. Drescher CW, Beatty JD, Resta R, et al. Effect of referral for genetic counseling on surgical prevention in women at high risk for ovarian cancer. Manuscript submitted for publication.

11. Tugwell P, de Savigny D, Hawker G, et al. Applying clinical epidemiological methods to health equity: the equity effectiveness loop. *BMJ.* 2006;332:358-61.

12. O'Neil J, Tabish H, Welch V, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *J Clin Epidemiol.* 2014;7:56-67.

13. Lornec T, Petticrew M, Welch V, Tugwell P. What types of interventions generate inequalities? Evidence from systematic reviews. J Epidemiol Community Health. 2013;67:190-3.

14. Mechanic, D. Disadvantage, inequality, and social policy. Health Aff (Millwood). 2002;21:48-59.

15. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Bethesda, Md.: The Commission, 1978. Print.

16. Phelan JC, Link BG, Feldman NM. The genomic revolution and beliefs about essential racial differences: a backdoor to eugenics? *Am Sociol Rev*. 2013;78:167-91.

17. Condit C, Bates B. How lay people respond to messages about genetics, health, and race. *Clin Genet.* 2005;68:97-105.

18. McAllister M, Davies L, Payne K, et al. The emotional effects of genetic diseases: implications for clinical genetics. Am J Med Genet A. 2007;143!:2651-61.

19. Khoury MJ, Evans JP. A public health perspective on a National Precision Medicine Cohort: balancing long-term knowledge generation with early health benefit. *JAMA.* 2015;313:2117-8.

ACKNOLWEDGEMENTS

First, thank you to my family for your love and support.

I would also like to acknowledge my Dissertation Committee and thank them for their guidance during this process.

Thank you to my previous and current mentors—I could not have gotten here without you.

To my colleagues at the FHCRC and classmates in the Health Services and Public Health Genetics programs—thank you for keeping me sane and answering my endless questions.

Finally, thank you to my amazing support system of friends.

I would also like to acknowledge *BMC Medical Ethics*, where paper one was originally published, and the following funding sources: R25CA92408, U54CA132381, U54CA153502, P50CA083636, RO1DK079042, 1R18DP001142.