Manuscript title: Knowledge about and patterns of genetic testing in newly diagnosed breast cancer patients participating in the iCanDecide Trial

Running title: Knowledge of breast cancer genetic testing

Authors: Michele Gornick[1], Allison W. Kurian, MD, MSc[2], Larry An, MD[1], Angela Fagerlin, PhD[3], Reshma Jagsi, MD, DPhil[4], Steven J. Katz, MD, MPH[1], Sarah T. Hawley, PhD, MPH[1]

[1] Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

[2] Department of Medicine, Stanford University, Stanford, California; Department of Health Research and Policy, Stanford University, Stanford, California.

[3] University of Utah, School of Medicine, Salt Lake City, UT;

[4] Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, Michigan

Corresponding author: Sarah T. Hawley, PhD, MPH, University of Michigan, North Campus Research Complex, 2800 Plymouth Rd, 4th Floor, Ann Arbor, MI 48109; e-mail: sarahawl@umich.edu.

14 text pages, including title page, references, and figure legends; 2 tables; and 3 figures

Precis for use in the Table of Contents: As interest in genetic testing increases, so will the need to integrate tools into the treatment decision process. Results from the current study suggest that while knowledge about the probability of a BRCA1 and/or BRCA2 pathogenic variant remains low in this patient population, the interactive decision tool improved rates relative to a static website.

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Keywords: BRCA1 and/or BRCA2, Genetic testing, decision-making, diagnosis, breast cancer patients, probability information, decision tool, knowledge

ABSTRACT

Background: This study reports rates of knowledge about the probability of a BRCA1 and/or BRCA2 pathogenic variant and genetic testing in breast cancer patients, collected as part of a randomized controlled trial of a tailored, comprehensive and interactive decision tool (iCanDecide).

Methods: 537 newly diagnosed, early-stage breast cancer patients were enrolled at the first visit in 22 surgical practices, and surveyed 5 weeks (N = 496; RR 92%) post enrollment after treatment decision-making. Primary outcomes include knowledge about probability of carrying a BRCA1 and/or BRCA2 pathogenic variant, and genetic testing after diagnosis.

Results: Overall knowledge about the probability of having a BRCA1 and/or BRCA2 pathogenic variant was low (29.8%). Significantly more intervention than control patients had knowledge about a BRCA1 and/or BRCA2 pathogenic variant probability (35.8% vs. 24.4%, $p < 0.006$). In multivariable logistic regression, the intervention arm remained significantly associated with knowledge about probability of having a BRCA1 and/or BRCA2 pathogenic variant (OR = 1.79, 95% CI 1.18-2.70).

Conclusions: Results suggest that although knowledge about the probability of having a BRCA1 and/or BRCA2 pathogenic variant remains low in this patient population, the interactive decision tool improved rates relative to a static website. As interest in genetic testing continues to rise, so will the need to integrate tools into the treatment decision process to improve informed decision-making.

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Complete List of Authors:	Gornick, Michele; University of Michigan, Internal Medicine Kurian, Allison; Stanford University School of Medicine, Medicine/Health Research and Policy An, Lawrence; University of Michigan, Center for Healthcare Communication Fagerlin, Angela; University of Utah School of Medicine, Population Health Sciences Jagsi, Reshma; University of Michigan, Department of Radiation Oncology Katz, Steven; University of Michigan, Internal Medicine Hawley, Sarah; University of Michigan, General Medicine Div. Ofc.
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[1] Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

[2] Department of Medicine, Stanford University, Stanford, California; Department of Health Research and Policy, Stanford University, Stanford, California.

[3] University of Utah, School of Medicine, Salt Lake City, UT;

[4] Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, Michigan

Corresponding author: Sarah T. Hawley, PhD, MPH, University of Michigan, North Campus Research Complex, 2800 Plymouth Rd, 4th Floor, Ann Arbor, MI 48109; e-mail: sarahawl@umich.edu.

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INTRODUCTION

Advances in genetic technology, particularly multigene panel testing, increase the clinical diagnostic and therapeutic uses of genetic testing in breast cancer. However, results from multigene panel testing add to already difficult decisions about next steps in clinical care soon after a breast cancer diagnosis. The addition of multigene panel testing to the decision-making process requires additional knowledge, consideration, and application of genetic risk information for the various treatment options. Given the association between genetic testing outcomes and treatment utilization, knowledge is critical. Yet, patient knowledge about breast cancer genetics and implications of genetic test results for different treatment options is low[1,2], further widening the gap between the availability of more expansive genetic testing and the usefulness of the results from genetic testing to treatment decision-making.[3-6]

Few tools have been developed for breast cancer-related decision-making that address important aspects of genetic testing on the implications of test results for treatment for individuals already diagnosed.[7] This is particularly concerning given a previous study found that the most commonly reported immediate post-diagnosis concerns are treatment and prognosis, followed by the probability of developing a second cancer, and the probability of developing cancer for family members.[8] Knowledge about the probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant, as well as the uses and benefits of genetic testing, in individuals with a family history of breast and ovarian cancer have been well described.[9,10] However, only three tools are specifically designed for women with a pathogenic variant, or those already diagnosed with breast cancer.[11-13] Further, knowledge about probability of *BRCA1* and/or *BRCA2* pathogenic variants and about the benefits and purpose of genetic testing in relation to treatment has not yet been assessed in breast cancer patients following diagnosis. Few studies have formally evaluated the role of genetic testing in breast cancer treatment decision tools

after a diagnosis of breast cancer. As there is no consensus on what should be covered across the various phases of the genetic testing process (e.g. health-related decision-making, results dissemination to family members), many tools lack important themes relevant to different points in the process.[11,14,15]

The purpose of this analysis, conducted after successful completion of a large randomized controlled trial assessing the effect of a decision tool (iCanDecide) on decision-making for locoregional breast cancer treatment, was twofold. First, we sought to determine whether breast cancer patients who viewed the intervention version of iCanDecide would have higher rates of knowledge about *BRCA1* and/or *BRCA2* pathogenic variant probabilities, benefits of breast cancer genetics, and implications of test results for treatment than those who viewed the control version. Secondly, we aimed to describe patterns of genetic testing use among participants of the iCanDecide study, recruited from community-based surgical practices in several states.

MATERIALS AND METHODS

Study design and patient recruitment

This study reports secondary analysis of data collected as part of a randomized controlled trial of a tailored, comprehensive and interactive decision tool (iCanDecide), compared with static online information[16]. The iCanDecide protocol and primary outcomes analyses have been published.[16,17] 537 newly diagnosed, early stage (0-II) breast cancer patients between the ages of 21 and 84 were enrolled at the first visit in 22 surgical practices in 4 states. After receiving an introduction packet from surgical practices, participants consented online, completed a short survey, and were allocated to a study arm using randomization stratified by site, age, race, education and timing of surgical consult. Eligible and consenting patients within

each practice were randomized to the intervention (tailored and interactive) or control (static information) version of the iCanDecide website. The primary outcome was a high-quality locoregional treatment decision (defined as an informed decision that was concordant with patients' values), with knowledge about genetic testing serving as a secondary outcome. Both were assessed from the first follow-up survey, mailed 4-5 weeks (N = 496; RR 92%) post-enrollment. A rigorous post-test design comparing intervention to control on primary and secondary outcomes was used to increases engagement with the website and reduce burden on the respondents associated with required baseline questions.[18] (iCanDecide intervention website available at: http://cansort.med.umich.edu/research/tools-and-resources/).

Measuring genetic testing knowledge

For the first objective of this analysis, the primary patient-reported outcomes measured included accurate knowledge about aspects of genetic testing: (1) probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant (correct/incorrect/didn't know), and (2) benefits and purposes of genetic testing after being diagnosed with breast cancer.

Knowledge about probability of carrying a BRCA1 and/or *BRCA2* pathogenic variant

Knowledge about probability of carrying a pathogenic variant was measured using an item designed by the study team. Participants were asked "Out of 100 women diagnosed with breast cancer, how many have a pathogenic variant in the breast cancer genes *BRCA1* and/or *BRCA2*?" Response options included: "Few (0-10 women)", "Some (11-25 women)", "Quite a few (26-50 women)", "Many (51-75 women)", "Most (76-100 woman)", or "Don't know." Responses were categorized as "Correct" for participants who selected "Few (0-10 women)" and "Incorrect" or "Don't know" for all other endorsed response options.

Knowledge about benefits and purposes of testing after being diagnosed with breast cancer

Knowledge about the benefits and purposes of genetic testing was measured using 3 questions developed and pilot tested by our clinical team to be consistent with the existing knowledge scales for locoregional and systemic treatment also being used in this RCT.[16,19]

Participants were asked if the purpose included: deciding how to treat, determining probability for a new breast cancer, prevention of future cancers, and informing family members' risk of breast cancer. Details about the survey questions are provided in the Appendix <SUPPLEMENTAL TABLE_1>.

Patterns of testing in the iCanDecide sample

At the follow up survey, participants were asked to provide information about genetic tests that they might have had as part of diagnosis or treatment for breast cancer or for cancer risk. Participants were provided a brief description of the purpose of genetic testing. Next, respondents were asked, "Did a doctor or other health professional talk with you about having a genetic test for breast cancer risk?" (yes/no/don't know), "Did you have a counseling session with a genetic counseling expert – that is, an appointment where the whole or most of the discussion is about genetic risk for breast cancer?" (yes/no/don't know), and "How much did you want to have a genetic test to tell you the risk of you or your family developing new cancers in the future?" (5-point scale from not at all to very much). Participants were then asked, "Have you ever had a blood or saliva genetic test for breast cancer risk that was ordered by a doctor?" If the participant endorsed that they had a doctor ordered blood of genetic test for breast cancer, they were asked about their perception about why the test was ordered, if they had the testing before or after diagnosis, and the result of the genetic testing. Exact timing of testing or counseling relative to the intervention was not known however, since participants could have been tested before or after viewing the website. Participants who did not have a doctor order a

multigene panel test were asked to select why they didn't have genetic testing for breast cancer.

Patient factors

Patient characteristics were obtained from patient report at log in and included age, race, education level, and partnership status. The initial survey also assessed whether the patient had seen her surgeon yet (yes/no).

Statistical methods

To assess genetic testing knowledge, we followed a pre-specified analytic plan[17] to assess whether rates of knowledge about both knowledge measures (probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant and knowledge about benefits and purposes of testing after being diagnosed with breast cancer genetic testing) were higher in intervention than control participants. Preliminary analyses to explore combining all items into one knowledge scale did not indicate one scale was appropriate. Internal consistency (Cronbach's alpha = 0.65) suggested internal reliability was not ideal, even after removing items with consistently low correlations ($r < 3$).

We used Chi-square tests and testing was two-sided, with a P-value of <0.05 considered statistically significant. Participants with missing values on the outcome measures or covariates (<5%) were excluded from the analysis. In post-hoc analyses, we used logistic regression to model the association between study condition and both dichotomous knowledge outcomes adjusting for patient factors that were significant in bivariate analyses, as well as study site.

To describe patterns of genetic testing in this clinical sample, we generated descriptive statistics regarding patterns of genetic testing and discussion, reasons for the provider-ordered genetic test, and participant-reported result of the testing.

RESULTS

Participant characteristics

Study packets were distributed to 1,084 patients, of whom 567 (52.3%) visited the website and nearly all of these (537, 94.7%) were eligible, created an account and completed an enrollment survey[16] <FIGURE 1>. Response rate to the first follow-up survey was 92% (N=496) in both intervention and control (N=245 intervention, 251 control). The study arms were balanced with regard to demographic factors <TABLE 1>.

Genetic testing knowledge

Knowledge about probability of carrying a BRCA1 and/or *BRCA2* pathogenic variant

Overall, the rate of knowledge about the probability of having a *BRCA1* and/or *BRCA2* pathogenic variant among women diagnosed with breast cancer was low (29.8%) when measured 5 weeks after the first surgical visit and after treatment decision-making had occurred. In bivariate analyses, significantly more intervention than control patients had knowledge about *BRCA1* and/or *BRCA2* probability (35.8% vs. 24.4%, p = 0.006). In an adjusted multivariable model, patients who viewed the intervention had higher odds than the control group of correctly answering the question about probability of having a *BRCA1* and/or *BRCA2* pathogenic variant (OR = 1.79, 95% CI 1.18-2.70) <FIGURE 2>. Other factors significantly associated with odds of high knowledge including higher education levels (OR = 2.78, 95% CI 1.46-5.27). Compared to participants who self-reported as white, black patients were less likely answer the question about the probability of having a *BRCA1* and/or *BRCA2* pathogenic variant

correctly (OR = 0.29, 95% CI 0.14-0.60). Older individuals were less likely than patients under 49 years of age to answer correctly (57-65 years old OR = 0.44, 95% CI 0.23-0.73; >65 years OR = 0.33, 95% CI 0.18-0.60).

Knowledge about benefits and purposes of testing after being diagnosed with breast cancer

Patient knowledge about the benefits and purposes of genetic testing for treatment decision-making was generally high (% correct for each question; Range 72.49%-89.20%). In bivariate analyses, the only item for which there was a significant difference in correct response between intervention and control subjects was about whether the purpose of getting *BRCA1* and/or *BRCA2* genetic testing after a diagnosis of breast cancer is to help a woman know whether her family members may be at risk for getting breast cancer (95.51% vs. 89.21%, respectively; p = 0.023).

This association held in multivariable logistic regression (OR = 2.75, 95% CI 1.18-6.43) <FIGURE 3>.The only other factor significantly associated with higher odds of knowledge of benefits and purposes included higher education level (OR = 2.78, 95% CI 1.22-6.34). There were no differences by arm in the proportion answering the other knowledge questions correctly.

Patterns of testing in the iCanDecide sample

The majority (71%) of survey respondents said that a health care professional spoke with them about having a genetic test for breast cancer risk. However, less than half (42%) reported having a counseling session with a genetic counseling expert. Fifty-six percent of respondents endorsed that they wanted to have genetic testing to tell him/her about the risk of future cancers either “quite a bit” or “very much”. The percentage of respondent that spoke with a health care professional about having a genetic test, and the percentage of respondent who endorsed that they wanted to have a genetic test did not vary by state of surgical practice.

However, a chi-square test of goodness-of-fit determined the frequencies of respondents reported having a counseling session with a genetic counseling expert was higher if the surgical practice was in the state of Georgia than the other 3 states X^2 (9, N = 496) = 21.14, $p < 0.04$. Among tested patients (n = 196), 95.41% had testing after being diagnosed with breast cancer. Seventy-three percent said that no pathogenic variant was detected, 3.57% stated that they had a pathogenic variant in *BRCA1* and/or *BRCA2* or another breast cancer risk-associated gene, 7.56% reported a genetic variant of uncertain significance was detected, and 8.67% did not know the results of genetic testing.

Untested participants (N = 254) randomized to the intervention group had higher knowledge than control subjects. However, the sample size is too small to detect an interaction between testing and assigned group in the multivariable logistic regression model.

The most commonly selected reasons for getting tested were: "My doctor thought I should" (78.57%), "I wanted to get more information about my own health" (70.41%), "I wanted to get more information for my family member" (68.88%). Among those *not* tested (N =278), the most frequently endorsed (59.71%) reason for not having genetic testing done was that "my doctor did not recommend it," similar to previous reports[5] <TABLE 2>.

DISCUSSION

The results of this randomized controlled trial conducted in a large clinical sample of women with a new diagnosis of breast cancer suggest that a decision tool can improve components of knowledge about genetic testing. Patterns of testing in this sample were similar to those in larger population-based samples,[5] and many women reported they had not received formal genetic counseling. Although we did not know the timing of counseling relative to study participation, this result confirms findings from population-based studies suggesting there may be opportunities for tools to be integrated into the clinical workflow to educate patients about

the availability and information that can result from having genetic testing.[5,20] Prior studies have suggested that patients' recollection and interpretation of complex information (e.g. pedigree-based hereditary likelihood) may differ from what was discussed during a genetic counseling session.[21-25] Given that verbal information during counseling alone may be inadequate, interactive decision tools are one possible way to enhance and improve patients' knowledge, and interpretation of information about *BRCA1* and/or *BRCA2* genetic testing. The potential for online decision tools to help address patient information needs in this complex area is therefore particularly compelling. Although not a replacement for professional advice, our findings suggest that online tools can provide a useful complement.

Although most newly diagnosed breast cancer patients are unlikely to carry a high-risk cancer pathogenic variant, the growth of testing options and increase in accessibility of testing underscore the importance of ensuring that all individuals have accurate knowledge about what the test(s) do, not just those who opt to receive genetic testing.[26,27] While overall knowledge about probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant was low in this population, the interactive decision tool was associated with higher knowledge about the higher knowledge about this probability, and some benefits and purposes of genetics testing after being diagnosed with breast cancer, compared to a static website. The improvement in aspects of knowledge after interaction with the iCanDecide intervention indicates that the integration of clinical decision support tools into the breast cancer treatment decision process can provide additional support to patients. The 11.4% increase in genetic testing knowledge observed in this study is promising particularly since genetic testing was not the primary focus of the iCanDecide website. Despite this positive finding, the overall rates of knowledge even in the intervention arm were relatively low (11.4%) suggesting the opportunity for further work to improve knowledge about genetic testing. Importantly, prior work assessing knowledge improvements

about locoregional treatment in this population similarly found the need for improvements in knowledge.[16] This work, as well as other reports[28-30] show low knowledge in breast cancer patients even after treatment. Persistent low knowledge along with the fact that it remains unclear what is clinically meaning in this context, underscores the need for interventions focusing on enhancing knowledge using novel and engaging methods. Tools that offer the ability to link with clinicians, or the clinical system, could be useful in providing clinicians with additional opportunities to close the loop with patients even after interacting with a decision tool.

Results from the current study indicate that patients have generally high knowledge about the probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant after being diagnosed with breast cancer, and we did not observe an intervention effect on this type of knowledge, with the exception of the need to test in family members. While overall knowledge of these items may be high in patients with a new breast cancer diagnosis, the potential to influence knowledge about the need to test family members suggests an area where tools may be particularly useful. However as noted above, our results suggest that there is still considerable room to improve the knowledge about probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant, particularly in older individuals and patients with less education. This is also important, given the implications of having a *BRCA1* and/or *BRCA2* pathogenic mutation for testing in family members, and cascade testing to identify individuals who may be at risk for getting breast cancer. Future work addressing other factors that contribute to lingering knowledge deficits. These areas of enhancement include addressing emotional issues (anxiety and worry) that can contribute to the ability to truly comprehend cognitively, and providing educational materials to the provider that highlight remaining knowledge deficits.

The participants in this study are unique in the sense that this is a clinical sample of newly diagnosed breast cancer patients recruited at the time of making their surgical treatment decision, likely reflecting what is happening in the current clinical context. The majority of participants in our study reported that a health care professional spoke with them about having a genetic test for breast cancer risk. Our patterns of testing are similar to our prior recent report in a population-based sample of patients with breast cancer.[6] Yet, also similar to population based data, we found that fewer than half reported having a counseling session with a genetic counseling expert. Although sufficient pre-test counseling could have occurred by other means, this finding suggests that the majority of patients did not receive optimal pre-test discussions about genetic testing. This could also be a result of an insufficient genetic counseling workforce nationwide.[14] Providing further support for tools that address key aspects of genetic testing such as ours.

These findings are consistent with the broader literature on the potential positive impact of interactive online decision aids. Trials have demonstrated improvements in understanding of prognosis, treatment options, decisional conflict, and satisfaction with the use of decision aids in breast, as well as other cancers such as colorectal, and thoracic oncology.[31-34] Further, decision aids have been shown to weigh the absolute magnitude of benefit against competing risks and ideally align choices more closely with the individual patient's personal preferences, particularly in the context of genetic testing.[13,35]

Study strengths include a large, diverse sample, detailed information on patterns of genetic testing, and a high participation rate. Limitations include self-report of genetic test results which may be subject to recall bias. Although we achieved good representation of patients across subgroups, there remain limits to generalizability to all racial and socioeconomic

groups, and non-response might have biased results. Given the importance of genetic testing to treatment decisions for patients and family members, further work is needed to understand what clinically meaningful differences in knowledge about genetic testing would be from the perspective of clinicians who care for breast cancer patients. Finally, it is important to note that this study was conducted prior to the widespread adoption of multiplex testing, and therefore focused on individual gene testing. However, we suspect that limitations in knowledge will only be exacerbated by multiplex testing.

As the scope of and interest in genetic testing continues to rise, an already scarce genetic counseling workforce is increasingly taxed.[3,5,6,14] Offering patients decision support tools that educate them about genetic testing and its relevance to the breast cancer treatment decision-making process may be a promising method for supplementing and supporting genetic counselors. Tools can be used to deliver key information to patients, tailored to their risk and interest in genetic testing, that can be useful in directing the clinical resources for counseling and testing. Moreover, tools can be used to inform patients regarding the need for family involvement and education about genetic testing. Additionally, tools that can help to calculate probability of pathogenic variant carriage and interest in testing prior to meeting with genetic counselors may help to tailor discussions appropriately. Yet the existence of knowledge gaps even after tool viewing underscores the importance of continued work to engage clinicians in the process of educating patients through integration of tools into the clinical and genetic counseling workflow to support the growing complexity of breast cancer treatment decision-making.

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Figure Legend

Figure 1: iCanDecide study patient participant recruitment diagram

Figure 2: Results from logistic regression model on the likelihood of correct response to the knowledge question regarding the frequency of woman with a pathogenic variant in *BRCA1* and/or *BRCA2* who were already diagnosed with breast cancer.

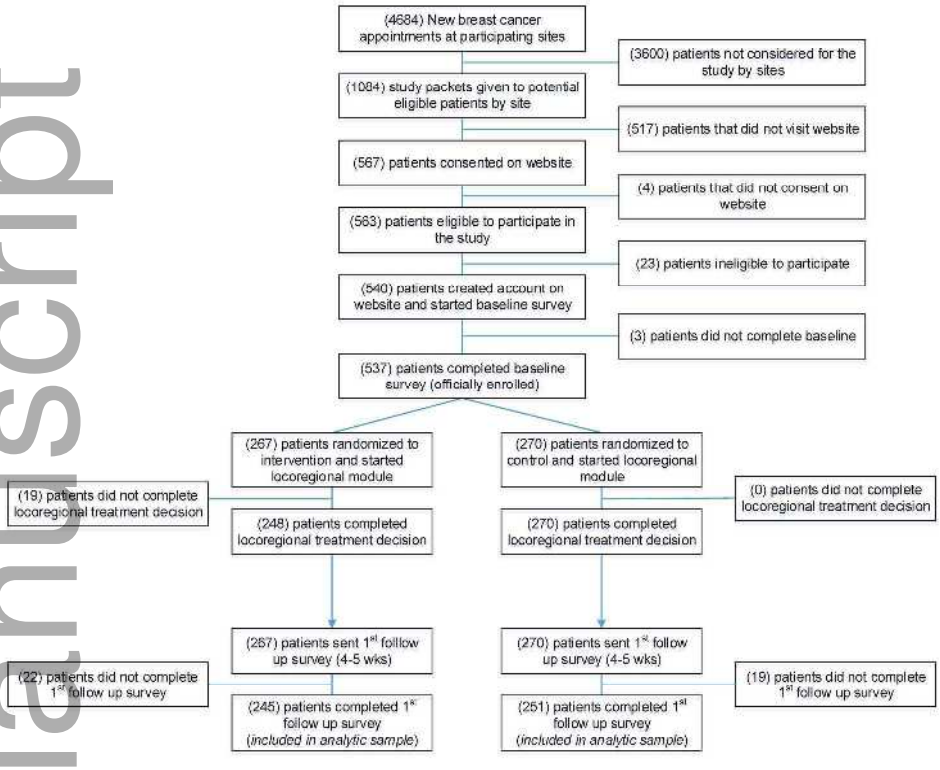
Figure 3: Results from logistic regression model on the likelihood of correct response to whether getting BRCA genetic testing after a diagnosis of breast cancer helps a woman know if her family is at risk of getting breast cancer.

Supplemental Table: Knowledge by intervention and control arm				
Knowledge about probability of carrying a *BRCA1* and/or *BRCA2* pathogenic variant	**Overall % Correct**	**Intervention % Correct**	**Control % Correct**	**P-value**
Out of 100 women diagnosed with breast cancer, how many have a pathogenic variant of the breast cancer genes *BRCA1* and *BRCA2*??	148 (30.08)	87 (35.81)	61 (24.40)	*0.0058*
Knowledge about benefits and purposes of testing after being diagnosed with breast cancer	**Overall % Correct**	**Intervention % Correct**	**Control % Correct**	**P-value**
What is the purpose of getting BRCA genetic testing after a diagnosis of breast cancer?				
To help women decide how to treat their breast cancer	337 (69.39)	170 (34.34)	167 (33.74)	n.s.
To help determine a woman's probability for developing a new breast cancer	389 (78.59)	197 (80.41)	192 (76.80)	n.s.
To help women who are found to be at "high probability" consider ways to prevent further cancer?	416 (84.04)	210 (85.71)	206 (82.40)	n.s.
To help a woman know if her family members may be at probability for getting breast cancer	457 (92.32)	234 (95.51)	223 (89.20)	*0.0225*
Does removing the "other" breast—the breast without cancer—improve survival for women with a genetic pathogenic variant?	349 (70.51)	179 (73.06)	170 (68.00)	n.s.
Does removing the "other" breast—the breast without cancer—prevent the cancer from coming back for women with a genetic pathogenic variant?	178 (35.96)	94 (38.37)	84 (33.60)	n.s.

Table 1: Description of participant characteristics

Characteristic	**Control Arm (n=270)**	**Intervention Arm (n=267)**	**p-value**
	N (%) or mean (SD)	**N (%) or mean (SD)**	
Age	57.03 +/- 10.88 (270)	56.52 +/- 10.72 (267)	0.59
Race			0.89
White	212 (79%)	210 (79%)	
Black	45 (17%)	42 (16%)	.
Other	13 (5%)	15 (6%)	.
Education			0.89
High school graduate or less	58 (21%)	57 (21%)	
Some college/ college graduate	145 (54%)	148 (55%)	.
Some/completed graduate school	67 (25%)	62 (23%)	.
Married/Partnered			0.08
No	83 (31%)	64 (24%)	
Yes	187 (69%)	203 (76%)	.

Table 2: Participant patterns of testing for breast cancer			
iCanDecide survey question	**Overall % Endorsed**	**Intervention % Endorsed**	**Control % Endorsed**
Did a doctor or other health professional talk with you about having a genetic test for breast cancer probability ?	335 (70.97)	164 (69.79)	171 (72.15)
Did you have a counseling session with a genetic counseling expert – that is, an appointment where the whole or most of the discussion is about genetic probability for breast cancer?	203 (42.12)	99 (41.08)	104 (43.15)
How much did you want to have a genetic test to tell you the risk of you or your family developing new cancers in the future? [quite a bit or very much]	281 (56.65)	142	139
Have you **ever** had a blood or saliva genetic test for breast cancer risk that was ordered by a doctor?			
Why did you get tested:			
My doctor thought I should	154 (78.57)	79 (79.00)	75 (78.13)
I wanted to get more information about my own health	138 (70.41)	72 (72.00)	66 (68.75)
I wanted to get more information for my family members	135 (68.88)	69 (69.00)	66 (68.75)
Because of my family history	104 (53.06)	55 (55.00)	49 (51.04)
My family wanted me to be tested	20 (10.20)	11 (11.00)	9 (9.38)
Other	15 (7.65)	5 (5.00)	10 (10.42)
When did you have the test?			
Before I was diagnosed	8 (4.08)	4 (4.00)	4 (4.17)
After I was diagnosed	187 (95.41)	96 (96.00)	91 (94.79)
What was the result			
I did not have any pathogenic variants in the gene tests	144 (73.47)	72 (72.00)	72 (75.00)
I had a pathogenic variant in a gene that increases probability of breast cancer (BRCA1 or BRCA2)	7 (3.57)	5 (5.00)	2 (2.08)
A gene pathogenic variant was found, but not one that has been shown to increase risk of BrCa	15 (7.56)	5 (5.00)	10 (10.42)
I don't know the results	17 (8.67)	10 (10.00)	7 (7.29)
Other	12 (6.12)	8 (8.00)	4 (4.17)



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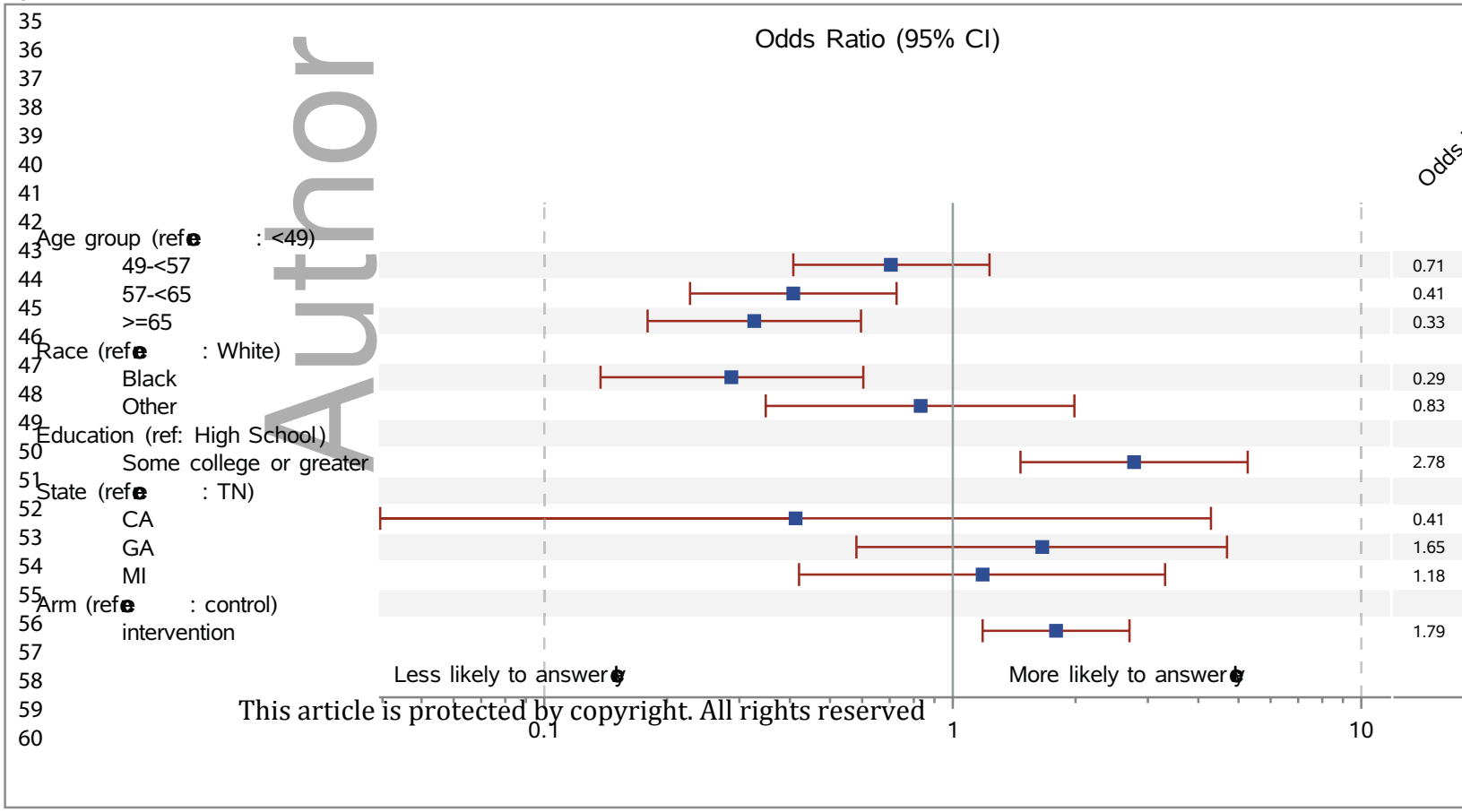

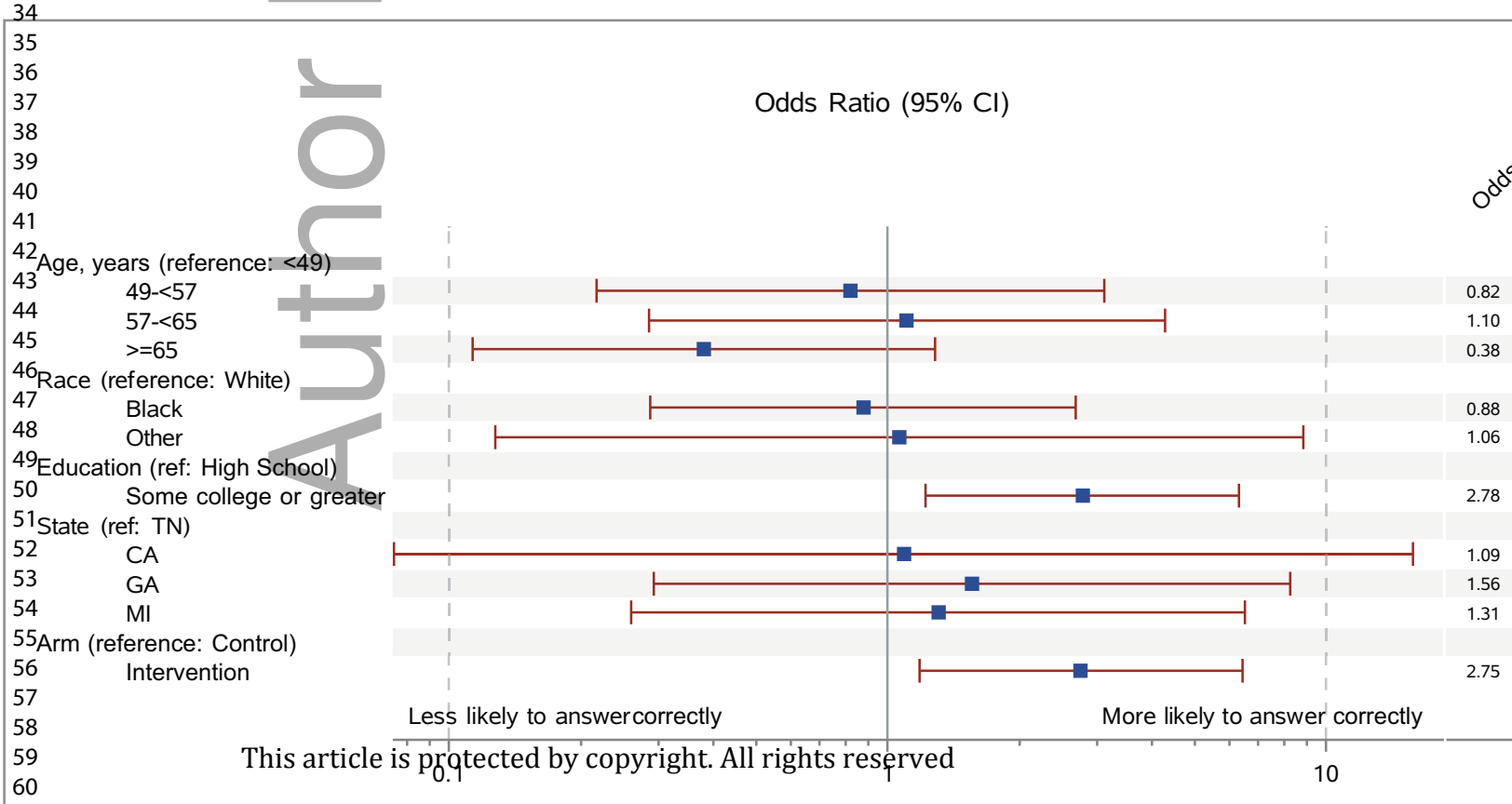

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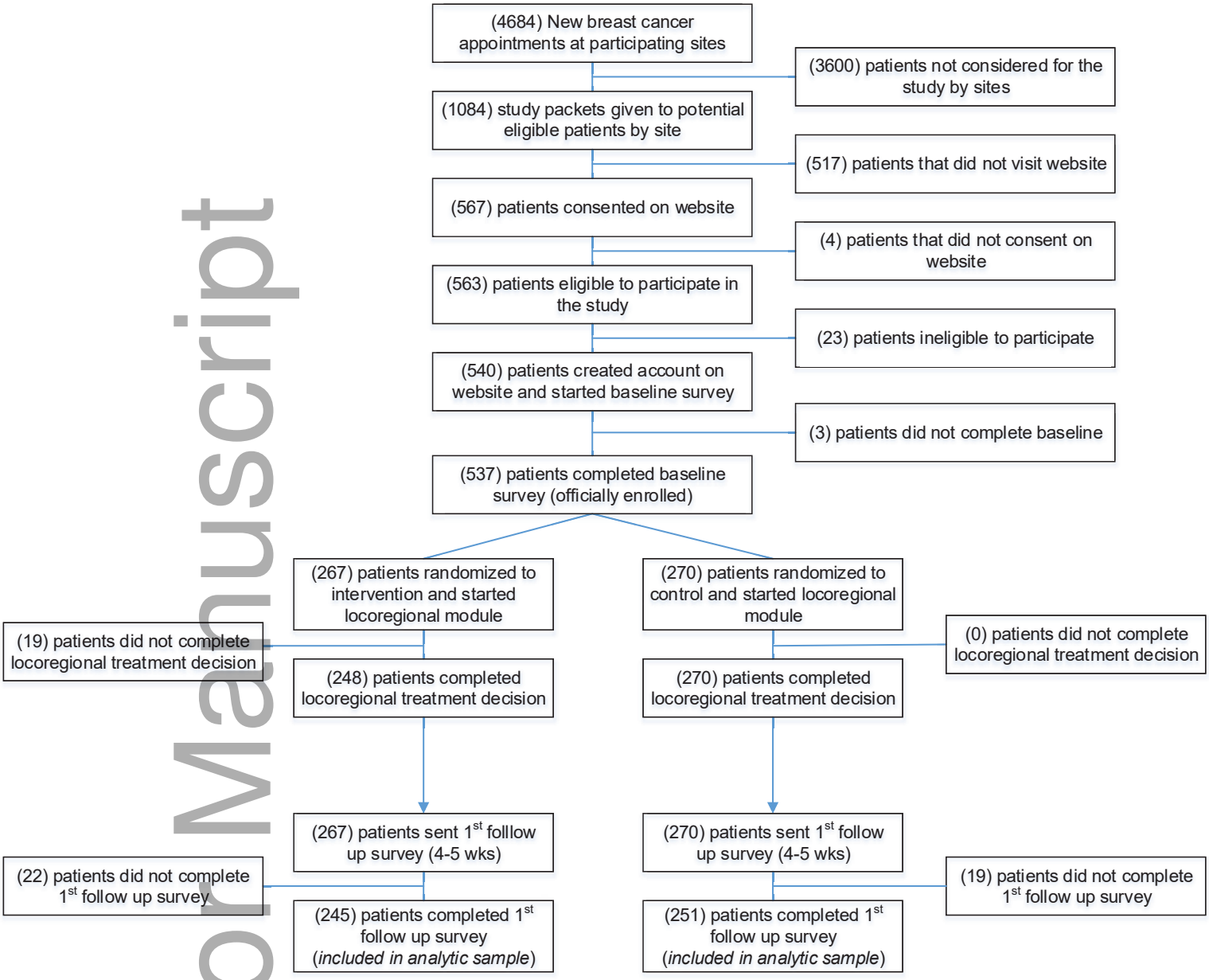

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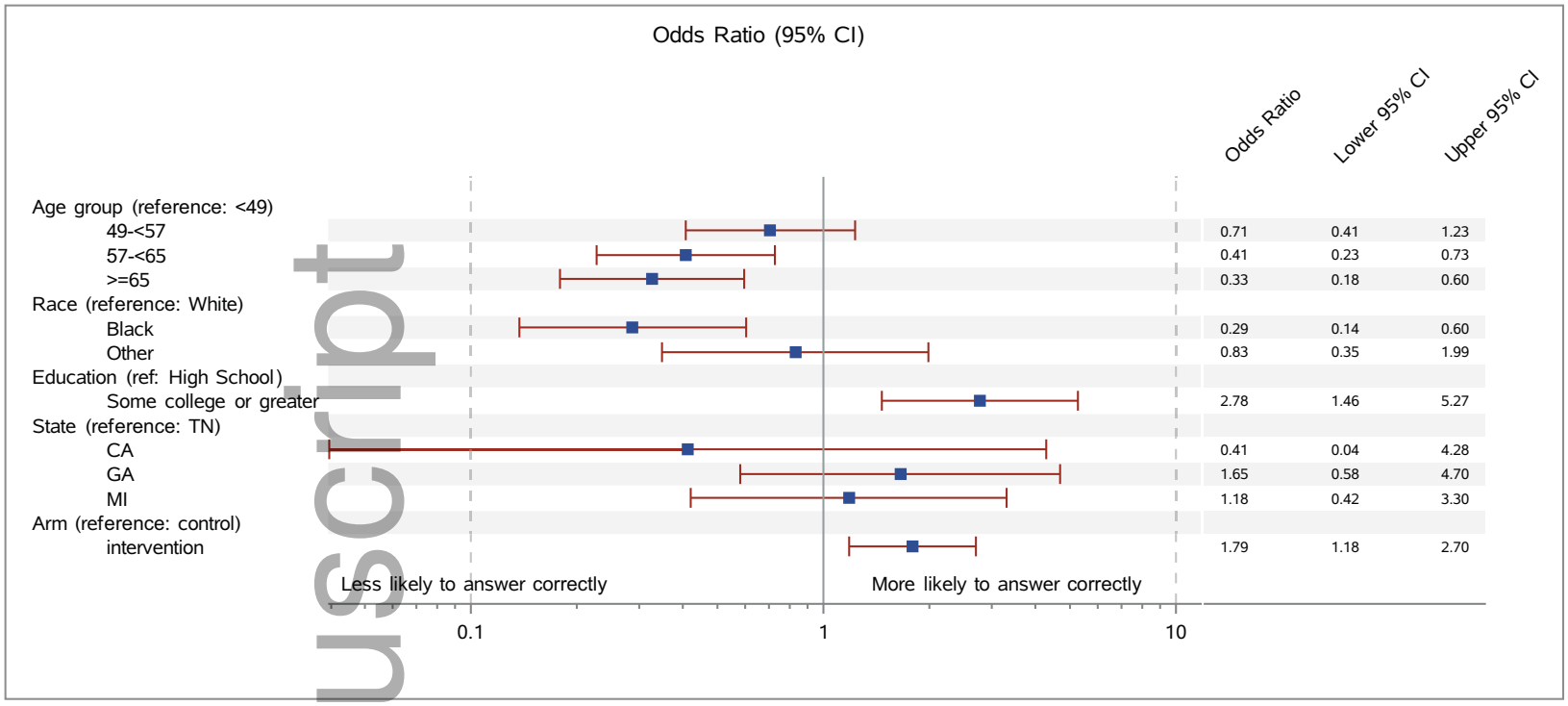

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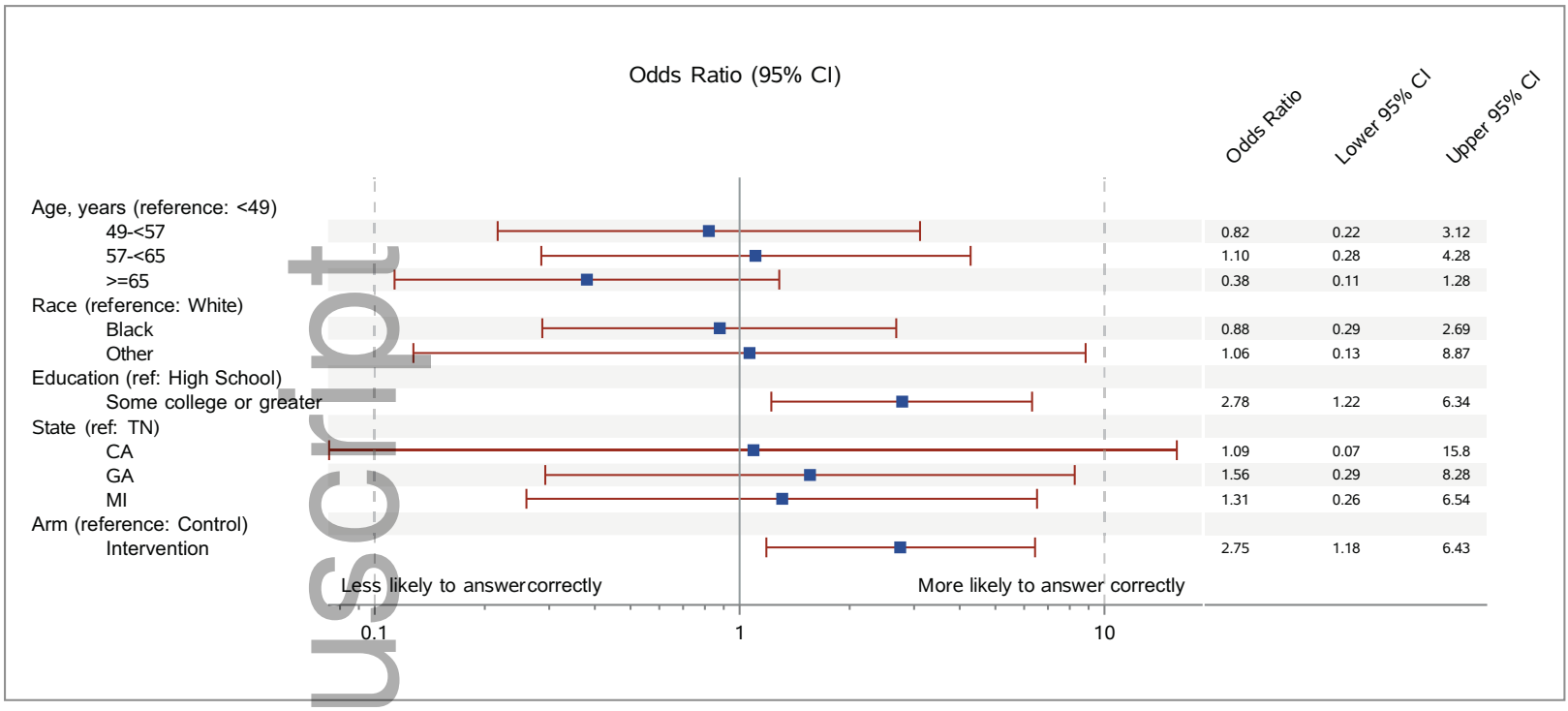

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