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Research Article

The Impact of Genetic Carrier Testing in Reproductive Decision-Making: *FMR1* Testing in Women with Diminished Ovarian Reserve

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Abstract

Background: This study examined how *FMR1* genetic testing impacts the reproductive decision-making of women with diminished ovarian reserve (DOR).

Methods: 120 women clinically diagnosed with DOR (elevated FSH and/or low AMH and/or low at trial follicle count, with regular menses), and without a family history of fragile X syndrome, received fragile X genetic testing (*FMR1*) and completed pretest questionnaires. A subset (n=7) were interviewed pretest. Surveys and interviews were analyzed separately and then integrated using sequential explanatory mixed methods.

Results: Approximately50% regarded carrying the *FMR1* pre mutation as a serious condition, while 37.5% had a neutral position. Women were significantly more likely to be upset about being a carrier if they perceived the *FMR1* pre mutation to be a serious condition ($p< 0.01$).Interviews reflect several inheritance concerns (immediate next generation, future generations, and extended family members) and the impact the test results might have on their future reproductive decisions.

Discussion: These qualitative/quantitative responses indicated that *FMR1* screening (1) informed DOR patients' view of an infertility diagnosis (2) prepared them for potential health consequences in future offspring and (3) impacted their future reproductive decisions.

ABBREVIATIONS

FMR1: Fragile X Mental Retardation 1; FXS: Fragile X Syndrome; DOR: Diminished Ovarian Reserve; POF: Premature Ovarian Failure; POI: Primary Ovarian Insufficiency

INTRODUCTION

Infertility affects approximately 9% of couples worldwide, or approximately 72 million women aged 20-44 years [1]. In the US, 12.1% of females aged 15-44 years have 12-month infertility or impaired fecundity, totaling 6.7 million women [2]. Forty-one percent of women with infertility/sub fertility seek assistance from fertility clinics [3]. Ten percent of women in an infertility clinic, totaling 275,000 women in the US, are diagnosed with DOR [4,5]. Reductions in oocyte quantity and quality with advanced age (typically themid-40s ages) are a normal physiologic occurrence termed diminished ovarian reserve (DOR)[6]. Some women experience DOR much earlier and become prematurely infertile (pathologic DOR).

Specific tri nucleotide repeat lengths in the fragile X mental retardation 1 (*FMR1*) gene (HGNC: 3775) are associated with ovarian dysfunction. Women with pre mutation level repeats in this gene (55-199 CGG) are at increased risk for premature ovarian failure (POF) [7-9], alternatively termed primary ovarian insufficiency (POI). The association of the *FMR1* gene with other forms of ovarian dysfunction such as pathologic diminished ovarian reserve (DOR) is less clear, as reviewed in 2014 [10]. These clinical diagnoses differ DOR is diagnosed by abnormal ovarian hormone levels and regular periods [11-13], while POF is diagnosed by postmenopausal levels of ovarian hormones plus 4 or more months of secondary amenorrhea before the age of 40 [14].

Some reports have suggested that women with "low normal" repeat lengths [15-17], or "high normal" and/or intermediate repeat lengths [18,19], including the pre mutation range [20,21], may be associated with DOR or infertility. Others have reported no association between *FMR1* repeat lengths and DOR [22] or

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infertility in general [23].

The American College of Medical Genetics testing guidelines recommend testing for pre mutation level *FMR1* genes in "women with reproductive or fertility problems associated with elevated follicle stimulating hormone levels, especially if there is a family history of POF, fragile X syndrome, or undiagnosed mental retardation" [24], which encompasses the definition of DOR. The National Society of Genetic Counselors and the Genetics Committee of the American College of Obstetrics and Gynecology support this recommendation [25,26]. Recommendations call for *FMR1* genetic carrier testing and pre-test genetic counseling for women with DOR [27].

Given these recommendations, more DOR patients will be undergoing genetic carrier testing who have no family history of fragile X syndrome (FXS), and are unfamiliar with its potential implications. A mother who carries a pre mutation level FMR1 repeat length has a 50% chance of passing the fully mutated gene (expansion to over 200 CGG repeats) to each of her children. Her children will either be pre mutation carriers or they will have the full mutation. The risk of passing on a full mutation is highest when at least one of the mother's *FMR1* alleles has over 100 CGG repeats [28]. Pre mutation carrier men will pass the pre mutation to all their daughters but none of their sons because men do not pass on their x chromosome. FXS symptoms include intellectual disabilities, attention deficit and hyperactivity, behavioral and learning challenges, sensory integration problems, and speech delays. Males are more frequently affected by FXS symptoms than females, and their symptoms are often more severe. Pre mutation carriers do not have FXS symptoms.

There is limited research on the cognitive and emotional reactions to and the impact on reproductive decision making from carrier testing for x-linked disorders. Carrier testing for autosomal and x-linked-recessive disorders has been associated with relief from fear and is useful in reproductive planning [29-31]. Relief from fear was reported whether they already had children (afraid they had put their children at risk to pass on the disease to grandchildren) or not (had feared having a baby with the disorder) [30]. A study of population screening for *FMR* pre mutations [33,34] found that while women had active coping mechanisms, they also had concerns for the implications of their carrier status for their children or grandchildren, the results impacted reproductive decisions whether in hindsight or for their own future, and the women's positive carrier status generally had minimal relevance unless it pertained to a current stage of life. Pre and post-test emotional reactions to *FMR1* testing among 20 women with DOR reported that participants anticipated that their self-esteem would be unchanged if their results indicated they carried the pre mutation, and most projected that if they did have the pre mutation they would feel better knowing there was a medical explanation for their infertility [35]. A qualitative study of seven women with DOR (using the same cohort as in this report) plus their spouses, reported that their pregnancy-seeking journey was long and exhausting, the expense of fertility testing/treatment was noteworthy, they understood the reproductive implications of carrying the *FMR1* pre mutation, and they hoped for a negative test result [29]. A related study [36] found that n=92 women diagnosed with DOR viewed the *FMR1* pre mutation as serious as women with a family history of fragile X syndrome [37]. For research related to the reaction to pre mutation screening among females with a positive family history of FXS, the reader is referred elsewhere [37-41].

This investigation began with the broad research question "how do women struggling with infertility approach genetic carrier testing in their reproductive decision-making?" Using a mixed methods analysis, the intent of this paper is to assess the impact of *FMR1* carrier screening and the anticipated test results on reproductive decision-making among women diagnosed with DOR.

MATERIAL AND METHODS

Overview and quantitative analysis

This is a post hoc analysis of data previously collected for the purpose of assessing the association between *FMR1* repeat lengths and DOR. For this report, the study hypotheses were generated prior to the analysis. The focus of this investigation was how and to what extent the *FMR1* genetic carrier testing (1) informed an individual's view of her infertility; (2) prepared her for the potential health consequences for future biological children; and (3) impacted her reproductive decision-making.

Mixed methods study design

Using a version of Creswell's sequential explanatory design for mixed methods research [42], collection and analysis of quantitative data was followed by the collection and analysis of qualitative data. The qualitative interview results were interpreted as a way to validate and expand upon the initial quantitative findings [42-44]. The source of the quantitative data was the FRAXELLE Study, which using a longitudinal multicenter cohort, investigated (1) the distribution of tri nucleotide repeats in the *FMR1* gene among women diagnosed with DOR and (2) the emotions towards testing for and potentially carrying the fragile X pre mutation. For qualitative findings, longitudinal interviews were conducted among a subset of the FRAXELLE Study participants. The quantitative and qualitative results were analyzed separately and integrated at the point of data interpretation.

This investigation only included baseline survey data from participants (after consent and the blood sample were drawn, but prior to learning the results of the *FMR1* carrier test). Similarly, while the FRAXELLE Study had conducted three longitudinal interviews, only the initial interview was included in this analysis (after consent and the baseline structured questionnaire was completed, but prior to learning the *FMR1* test results).

Quantitative data collection -participants and tools

A total of 120 women clinically diagnosed with DOR, and without a family history of FXS, provided blood for *FMR1* testing and completed baseline questionnaires. Women were excluded if there was a known cause of elevated follicle stimulating hormone (FSH) for one's age unrelated to fragile X, or a family history of FXS. Study details have been previously published [18,36]. Participants were enrolled between March 2005 and December 2013 through academic Reproductive Endocrinology and Infertility clinics at University of Virginia (UVA, 15.00%),

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Stanford University (35.83%), and University of North Carolina at Chapel Hill (UNC, 15.83%), as well as private fertility practices in Virginia (29.17%) and North Carolina (2.50%). Two women (1.67%) self-referred into the study. This study was approved by the Institutional Review Board at all academic sites (#11448 UVA, #11-1535 UNC, #16182 Stanford University).

At baseline, participants completed two questionnaires. The Primary Questionnaire assessed demographics, and infertility/reproductive history. The Emotions Questionnaire assessed the (1) perception of seriousness regarding fragile X pre mutations as a medical condition; (2) predicted level of impact a positive test result would have on reproductive decision-making; (3) level of upset at the potential for health consequences for future offspring; (4) importance of having a medical explanation for their infertility; and (5) Health Orientation Scale [45]. The 11-itemHealth Orientation Scale (HOS; "How would you describe your feelings at this moment when you consider that you are potentially a carrier of a fragile X pre mutation?") contains semantic differential items anchored with a negative and a positive adjective (e.g., "bad" and "good") corresponding to a score of 1 or 9, respectively, on a numbered scale [45]. See related reports for further details on the Emotions Questionnaire [32, 35, 36, 46].

Quantitative data analysis

All emotional reactions and opinions were measured using 9-point scales in which 1 = "not at all", 5 = "neutral", and 9 = "very much". The Shapiro-Wilk W test indicated that the majority of the categories were not normally distributed. Therefore, Wilcox on signed rank nonparametric statistics were used to analyze these scaled questions with paired results [47]. All items tested for potential effect modification by parity (0 vs. 1+ live birth) used Wilcox on signed rank tests. All statistical analyses were based on two-sided tests with an alpha of 0.05 and 95% confidence intervals using SPSS software version 21.

As consistent with previous research by Pastore et al. [36], three categories of response to "how serious do you think fragile X pre mutations are as a medical condition?" were created: "not serious" (response ≤ 3), "neutral" (response of 4, 5, or 6), and "serious" (response of ≥ 7). *A priori* analyses designed to stratify by the perception of *FMR1* pre mutations being a serious medical condition (response ≥ 7) versus those who did not (response ≤ 6) used exact Mann-Whitney U tests for nonparametric independent samples.

RESULTS

Quantitative study

Sample description: Among the full sample that completed the questionnaires, the mean age at study participation was 38.0 years and the mean age at initial DOR diagnosis was 36.6 years (Table 1). Participants were primarily Caucasian (73.3%), with a sizeable minority of Asian women (18.3%). While 80% of participants had not given birth, almost two-thirds had been pregnant at least once.

Characteristics of the qualitative interviewees mirror the characteristics of the larger study population, with the exception that all interviewees were Caucasian. Six of the interviewees were married and 1 was single. Three of the interviewed women had never been pregnant, 2 had been pregnant once but had not given birth, 1 had been pregnant twice but had not given birth, and 1 had conceived once with fertility treatment resulting in a live birth. For further detail, the reader is referred elsewhere [48].

All of the women had tried multiple fertility treatments to achieve a pregnancy; of the 6 interviewed women who reported their treatment history in the structured questionnaire, all had used oral and/or inject able fertility medications, all had used intrauterine insemination, three had used IVF, and none had used a donor egg.

Quantitative results

As shown in Figure (1), 61 participants (50.8%) regarded carrying the *FMR1* pre mutation as a serious condition, while 45 participants (37.5%) had a neutral position, and only 14 participants (11.7%) did not consider this a serious condition.

Table 1: Characteristics of the participants (n=120).

Factor	N (%)
Age at initial DOR diagnosis (years)	Mean 36.6 (sd 4.0) Median 37.8 Range 25-42
Age at study (years)	Mean 38.0 (sd = 4.3) Median 38.5 Range 26-49
Race: White Black Asian Mixed race/Other Hispanic Ethnicity	88 (73.3%) 4 (3.3%) 22 (18.3%) 6 (5.0%) 8 (6.7%)
Nulliparous (n=106) Nulligravid (n=111)	85 (80.2%) 42 (37.8%)
Smoking History Ever Smoked Regularly Current Smokers	 17 (14.2%) 2 (1.7%)

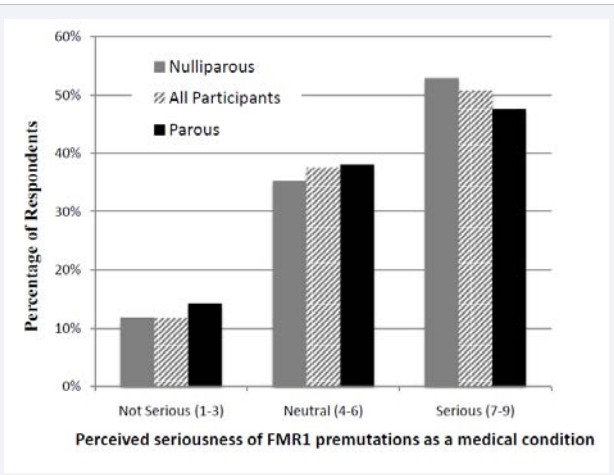

Figure 1 How serious do you think fragile X premutations are as a medical condition?
Nulliparous (n=85). Parous (n=21). Parity missing for n=14.

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While no significant differences by parity (p=0.664) were found by the Exact Mann-Whitney U test, we noticed a potentially interesting skew in responses. Specifically, a higher percentage of nulliparous participants regarded the *FMR1* pre mutation as a serious medical condition (response ≥ 7) than did the parous participants.

In response to the question "Without knowing your test result, how would you describe your feelings at this moment when you consider that you are potentially a carrier of a fragile X pre mutation?" participants reported feeling not guilty and un ashamed for the most part (Table 2). They predicted they would still feel not guilty and unashamed if they were found to carry the pre mutation. The lowest mean scores (most negative emotions) were reported on the bad/good and sad/happy subscales for both baseline and imagine positive emotions. Mean scores on each component were significantly higher (more positive) for baseline emotions than for imagine positive emotions ($p< 0.01$). Mean scores between baseline emotions and imagine positive emotions had an average differential of 0.86. No significant differences were found by parity (data not shown). However, significantly more negative emotions were observed for 6 out of the 11 components at baseline items (bad/good, afraid/unafraid, relieved/shocked, happy/sad, able/unable, and pleased/angry) when stratified by perceived seriousness of fragile X pre mutations ($p< 0.05$, data not shown).

At baseline, an overwhelming majority (80.7%) of participants agreed (response of ≥ 7) with the statement "I am glad to know there may be a medical reason for my infertility". Nulliparous participants were significantly more likely to agree with this statement than parous participants ($p< 0.05$). No significant differences were observed after stratification by perceived seriousness ($p> 0.05$).

In response to the question: "Genetic diseases are passed from parent to child. How upsetting would it be if you found out that fragile X runs in your family and that you could have a child or grandchild with fragile X?", the majority (61.5%) of participants reported that they would be very upset (response of ≥ 7, Table 3). Only 10.3% of participants said that this knowledge would not upset them (response ≤ 3), and 28.2% had a neutral position. Participants were significantly more likely to be upset if they perceived the *FMR1* pre mutation to be a serious medical condition ($p< 0.01$).No significant differences were observed by parity ($p> 0.05$).

The following scaled question was only asked of nulliparous study participants (n=81 for this item): "If you were found to be a carrier, do you think this would influence how you might feel about potentially never having had a child?" Responses were nearly equal across the three categories (38.3% responded "makes me feel better", 35.8% "neutral", and 25.9% "makes me feel worse"). There was no significant difference by perceived seriousness ($p> 0.05$).

MATERIAL AND METHODS

Qualitative analysis

Participants and interview study design: The FRAXELLE Study conducted a baseline interview with a subset of seven female participants, all of whom resided in North Carolina or Virginia. Women were selectively recruited to represent a range of tri nucleotide repeats [48], because it was theoretically possible that women could have different emotional reactions if they had FMR1 repeat lengths in the intermediate range as opposed to the normal range. For anonymity, the interviewees were coded (W1-W7). The sample size was based on data saturation [48,49]. As previously reported, all interviews were conducted by phone, and lasted 20-30 minutes [48]. The interview structure (Table 4) was based on a framework of anticipated narrative content, with probes adapted from previous research [33]. In order to allow individuals to speak fluidly about his/her experience, interviews followed a semi-structured format. The trained interviewers were instructed to use probes only when necessary to encourage participant elaboration [43,48].

The baseline interview focused on her experience since her DOR diagnosis, her past fertility struggles, her perception of fragile X, and her future expectations. The researcher who was the primary analyzer of the transcripts for this investigation (EW) did not interview participants. One of the authors was also an

Table 2: Health Orientation Scale (Baseline versus Imagine Positive).

	Baseline (pretest)		Imagine Positive (pretest)		p-value[a]
	Mean	Standard Deviation	Mean	Standard Deviation	
Health Oriented Scale[b]					
Good	4.5	1.953	3.16	1.754	<0.001
Unafraid	5.16	2.514	4.14	2.551	<0.001
Not Guilty	7.18	2.081	6.5	2.463	0.001
Unashamed	7.43	1.965	6.71	2.388	<0.001
Strong	5.99	2.056	5.25	2.377	<0.001
Relieved	4.89	1.939	4.18	2.624	0.002
Happy	4.01	1.994	2.98	1.808	<0.001
Able	5.72	2.235	5	2.48	<0.001
Pleased	4.73	1.566	4.02	1.815	<0.001
Healthy	6.36	1.974	5.38	2.334	<0.001
Unstigmatized	6.34	2.156	5.46	2.476	<0.001

[a] p-value calculated from paired sign rank statistics
[b] 1=negative emotion, 9=positive emotion

Table 3: Relationship between how upsetting fragile X in their family would be ("if found out that fragile X runs in family and it could be passed on to future generations") and pretest perceived seriousness of fragile X permutations.

Emotion	Percentage who reported this emotion among participants who consider premutations serious[a]	Percentage who reported this emotion among all other participants[b]	p-value[c]
Upset	73.8%	47.4%	0.005
Neutral/not upset	26.2%	52.6%	

[a] n= 61 women in this category responded to this question
[b] n= 57 women in this category responded to this question
[c] Continuous variable used for statistical comparisons (exact Wilcoxon test)

Table 4: Framework of planned interviews of female participants (Interview 1)

1.	Her reaction to the diminished ovarian reserve (DOR) diagnosis.
•	What was your vision of your family before you tried to get pregnant?
•	How did you first learn that your ovaries may not be producing enough eggs?
•	What did you expect from seeing an infertility specialist?
•	How does the DOR diagnosis influence your future reproductive decisions?
2.	Her reaction to the possibility that there is a genetic cause for her infertility.
•	Genetic testing is a sensitive issue. One could imagine that some people would hesitate to get genetic testing. Did you have any hesitations? If so, would you describe to me what they were?
3.	Her perception of fragile X and the testing process.
•	After you had your blood drawn for the fragile X testing, how did you feel? What did you do afterwards? Did you talk to anyone about it?
•	Do you perceive the decision you made to be tested as different from other (non-genetic) testing decisions? Was getting your blood drawn for the fragile X test any different than an infertility blood test of your hormones?
4.	Her perception of children or childlessness in relation to genetics and fragile X in particular.
•	Has the possibility of fragile X or another genetic cause of your infertility changed the way you view having children? Not having children?
5.	The impact of infertility and the fragile X testing on significant relationships.
•	Did you discuss your decision to have fragile X testing with your partner?
•	How does your partner feel about you getting the fragile x testing?
•	How do you and your partner make decisions? Is it different when it comes to your reproductive health?
6.	Her decision to participate in this study
•	What do you hope to learn from being in this study? How might this influence your reproductive decision-making?

interviewer (MC), and she served as a mentor for the qualitative analysis, as described below.

Qualitative data analysis

The transcripts were subjected to a discourse analysis. Direct quotations from the interviews served as the main source of raw data for qualitative analysis [43]. As outlined by JJ Kockelmanns [50], the transcripts were read twice for familiarity before they were reread to identify "strips" that captured important aspects of an individual informant's story. Similar strips were sorted into categories, and transcripts were reread a third time as a validity check. Categories were considered "themes" across the sample if reported by multiple participants. The identified themes were subjected to mentor review for verification. Confirmed themes, sufficiently supported by qualitative data (raw quotations), were then used to provide context to quantitative findings. Mentor review was used to verify that the supporting quotations adequately met the study questions addressed by the quantitative data. Because the quantitative study was conducted on a larger sample of the target population first, followed by a qualitative study on a subsample, the study framework allowed for generalize ability of the findings [43].

RESULTS

Qualitative study

Theme 1: Positive test result would provide a desired explanation for their DOR diagnosis: Although they voiced that they did not want to test positive for the fragile X pre mutation, the majority of women viewed the study as a possible opportunity to uncover an explanation for their early ovarian aging, as mentioned in a previous article with this cohort [48]. The idea that a positive test result would provide a desired explanation for their fertility struggle was a significant theme expressed by five of the women interviewed.

One participant reported that the result would bring her comfort after years of inability to conceive without explanation. "We don't know what the issue is… Yes, it would be nice to have that answer... It would be nice to know in my head the result"

(W2). This same woman said that she was happy for the study because of the possibility for answers. "I actually feel, you know, kind of glad that the study came out and we get the chance to, you know, find out, you know, is there a pre mutation?" (W2). For another participant, the test would either provide an answer or rule out one more potential issue. "Either I'm going to be positive and that's going to give me an answer and then…we'll take another…direction for family wise. Or you know I don't have it" (W6). For further discussion on the concept of closure for these women, see Pastore et al [48].

Theme 2: Concerns for offspring health if woman carries the pre mutation: Worry about the potential health consequences biological children could face, either with FXS or infertility difficulties of their own, was common among participants. One woman said, "if we did have our own children that there would be additional health risks that they could face" (W1). Another woman mentioned that she was previously unaware of the severity of the FXS. "I understood that you know the child could have problems you know mentally and physically and all that but I didn't really know the extent of it" (W6). Since learning of the severity of the condition, she did not want to bring a child into the world with the condition. "I don't want to have a kid that would have it" (W6).

Theme 3: Concern over the multiple generational impact of a positive test result and possible impact on extended family members' children: The idea of creating a negative genetic legacy was concerning to many women. One woman was worried repeat expansion in the future. "I would be passing on a gene that would only amplify through the generations. And so that would absolutely give me pause" (W1). The only participant that already had a biological child expressed anxiety for her daughter's future children. "What are the chances that she [daughter] would pass it to a child, is it a definite?" (W3). Many participants expressed worry for what a positive test result would mean for their future children's children. One participant worried not only about having a child affected with FXS, but also about having a child that carried the pre mutation. "I still wouldn't want my [future] daughter to have to go through that in 20 years if she has a boy" (W7).

Several women expressed concern for other family members who were preparing to have biological children. One participant expressed concern for her brother's pregnant wife multiple times. "I didn't realize the implications it might have for my brother who, well, he's pregnant right now with a little girl" (W7). She continued to worry about the implications a positive test result would have on that future child. "So then their daughter has to go through this 20 years from now worrying whether or not she's going to end up with a boy…who is going to have a terminal disease" (W7). One woman mentioned that the information from the test would be helpful for her siblings. "I think it [test result] would also be helpful, um, I have an older sister, who has a four-year old. I also have a younger sister um, who's getting married soon and I know she wants to have children" (W3). Another participant repeatedly expressed concern for her younger cousins at reproductive age. "I have younger family members that I think about that you know... there may be implications for them as well" (W2).

Theme4: Testing caused participants to pause and reconsider reproductive plans: The process of genetic carrier testing caused participants to pause and re-evaluate their future plans for fertility treatment, as mentioned previously [48], but discussed in further detail here. Many of the participants projected that a positive result would cause them to change their future plans. "I mean I'd have to revisit my feelings when I get the results to be honest" (W4). "It would make me sit down and do a lot more research on what the chances in passing it on were. I'd say that for sure" (W7). Another said that the results would affect upcoming reproductive choices in regards to fertility treatments. "I actually feel you know kind of glad…we get the chance to, you know, find out, you know, is there a pre mutation? Because we really figure our decision about do we continue to try on our own or if we do try on our own do we pay for pre-genetic testing, PGT…" (W2).

Some women were at a crossroad in their reproductive decision-making, and a positive test result was projected to influence their future decisions. One woman was previously considering moving from fertility drugs to injections. "The test results are going to…I already said that but that's going to make up – change our decision as far as, you know, having children on our own so" (W6).

Participants who were still trying to get pregnant using fertility treatments reported that a positive test result would influence how their IVF process would proceed (i.e.: using donor eggs instead of trying to use their own eggs). "I'm not sure I'd feel comfortable moving on with another IVF cycle without knowing those results…we just use that [positive test result] as part of our you know emphasis towards thinking maybe it's time to move to donor eggs" (W2). Using donor eggs would avoid the risk of passing the pre mutation or an expansion to a full mutation to the next generation [51]. "Well, if I knew I was the carrier I would probably definitely not use my eggs…." (W4). "People say why don't you adopt and I don't know if I'm ready to adopt. I guess the outcome of the study will be the interesting part for me if I learn genetically that some issues that would be, it will be easier to potentially use somebody else's eggs" (W4). After experiencing side effects with fertility drugs, one woman said, "For me I would say, gosh, adoption looks pretty amazing right now. Because I'm not averse to adoption now. So that [a positive test result] would make a case stronger" (W1).

DISCUSSION

Through our mixed methods analysis, three key points became apparent about how these women diagnosed with diminished ovarian reserve approach genetic carrier testing. First, participants searching for the cause of their infertility welcomed an explanation for their condition. The participants indicated a desire for accurate information about their *FMR1* results and their health and reproductive capacity even if the genetic test results held serious implications. Second, participants expressed strong concerns about potential health issues facing future biological children and the possibility of continuing a "negative" genetic legacy. Third, the process of having genetic carrier testing impacted the participant's reproductive decision making, and they projected that the results of the test could be a factor in weighing their future reproduction options. If they were

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found to carry the pre mutation, participants anticipated being willing to use donor eggs or adopt or to stop altogether efforts to have a future child. These observations were supported by both the quantitative survey data and the qualitative interviews.

Currently in clinical practice, only pre mutation carriers are routinely informed that their *FMR1* test results have relevance for reproductive decision-making. Some fertility clinics may also inform patients with intermediate repeat lengths ([45-54] CGG) of their risk of POI/POF (as reported in earlier reports [19,52,53] but not supported in more recent studies [54,55]) and/or the risk of expansion to a pre mutation in a subsequent generation (19% reported to either expand or contract in next generation [51]).

Research regarding the association between *FMR1* tri nucleotide repeat lengths and DOR is ambiguous as previously discussed, thus genetic counseling may not even mention this potential association. Pre implantation genetic diagnosis testing can be used to identify embryos at risk for FXS; this testing is much more common now than when our sample participated in this study. The prevalence of the pre mutation is 1:151 in the general female population in the US [56] (1:250 among women without a family history of FXS [57]**)**, and variation by ethnic heritage and country has been reported [58-60]. *FMR1* repeat length variation by ethnic heritage and country has also been observed within the normal range [61]. Given that most women affected by the recommendations for *FMR1* testing will receive negative test results, it is especially important to consider the emotional reactions to the testing process. This genetic test result may hold both welcome and unwelcome information for DOR patients: welcome in that an explanation for one's DOR may provide comfort and closure for infertile women, and unwelcome because such a diagnosis carries clear implications for reproductive decision-making and the potential health of offspring.

Genetic carrier testing informs participants view of DOR diagnosis

The way in which a genetic test result serves to inform participants' views of their diagnosis of DOR is contingent on individual factors, such as past fertility history, and the perceived seriousness of the genetic condition. Participants were significantly more likely to take comfort in a genetic explanation if they had never given birth. This observation is similar to that of a qualitative study of the general female population that found that the motivation for *FMR1* genetic carrier testing and the need for information differ by family history of FXS and parental status [33]. Another qualitative study of the impact on future reproductive decision-making from having a FXS offspring reported that the majority of mothers chose not to have another biological child, while 20% either purposely became pregnant or continued an unplanned pregnancy after finding out they carried the *FMR1* pre mutation [62]. In a commentary about population screening for genetic conditions including FXS, Archibald and Mc Claren [63], noted that initial judgments about the relevance of testing were centered on two key areas: reproductive state of life and health-related experiences. There is little prior research on the impact of previous parenthood with a healthy child on the neither emotional/psychological impact nor uptake of either prenatal or preconception genetic testing, thus this is an area ripe for future research.

The *FMR1* pre mutation testing is important for women at risk of carrying the pre mutation and still considering conception with their own eggs. Provision of information regarding a woman's chance of having a son or daughter with FXS or a daughter with the pre mutation is vital to her ability to make informed reproductive decisions. The quantitative data and qualitative interviews were consistent on the participants' concerns regarding inheritance of *FMR1* health effects and the legacy to future generations. Supporting our observation, others have reported that women with a family history of FXS more frequently reported a "concern for children" than a reproductive concern for themselves in structured interviews [37].

Genetic carrier testing impacts participants' reproductive decision-making

Reproductive decision-making is a multi-factorial process for any woman. The inclusion of a potential inherited condition into the equation magnifies the complexity of this process. The women with DOR in this study projected that the results of the genetic carrier test would be a factor in weighing their future reproduction options. Consistent with previous studies, the study population generally perceived the *FMR1* pre mutation as serious prior to testing, and recognized the medical importance of *FMR1* testing for their future fertility planning [32,48]. These patient reactions mirror those of women with a family history of FXS [37,38,64].Of the interviewed participants that were still undergoing fertility treatments, most were waiting for the results of the test before moving forward, implying that their next reproductive decisions would be contingent on the results they received. Our findings are consistent with previous research on the general female population, where participants "expressed that positive [*FMR1*] pre mutation results could have led to their reconsidering life plans especially their decision to have children"[33].

Not surprisingly, the participants who considered fragile X pre mutations to be serious had more negative baseline "imagine positive" emotions regarding this genetic testing. This suggests that both the testing process and the imagining of a positive result may be distressing for this population. Dealing with infertility, the population is already in an emotionally distressing situation. Although no other studies of the Health Orientation Scale in a pretest situation were located outside of our own prior research [35-46], carrier testing for autosomal and x-linked-recessive disorders has been associated with relief from fear and is useful in reproductive planning [30,31,48]. This relief from fear was reported whether they were parous (afraid they had put their children at risk to pass on the disease to grandchildren) or nulliparous (fear of having a child with the disorder) [30].

Strengths and limitations

Per the study protocol, participants had access to tailored educational materials and received genetic counseling prior to *FMR1* testing, which may limit the generalize ability because typical fertility clinics provide limited pretest genetic counseling. This study-provided genetic counseling may account for the

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participants' ability to understand the condition and the potential implications of a carrier result on future reproductive planning. This study is limited by its restriction to non-carriers, though our findings should be generalize able to women without a family history of FXS because the investigation analyzed pre-test emotions and both carriers and non-carriers enter the genetic testing arena without knowledge of their *FMR1* status. The lack of carriers in the population only allows for analysis of participants' predictions regarding the extent in which their reproductive decisions would be impacted if they were found to be a carrier; further investigation is needed to determine that the provision of a positive test result actually influences reproductive decision-making in carrier women without a family history of FXS. For literature on the impact on reproductive decision-making among women with a positive family history of FXS, see [62,64,65]. This study was limited to a patient population of women with DOR that sought input from a fertility clinic. It is further limited to women who chose to be tested for *FMR1*, and therefore may be more psychologically prepared or emotionally comfortable with undergoing genetic screening than the general population. As our study population was primarily white (with 18% Asian in the quantitative data and 0% minority races in the qualitative data), our results are limited regarding potential cultural differences in attitudes towards this genetic testing. Given the differences in the *FMR1* CGG repeat distribution by race-ethnicity in the pre mutation [58] and normal ranges [61], it would be especially interesting for future research to explore attitudinal variation on *FMR1* testing in OB/GYN clinics by heritage, similar to analogous research on prenatal genetic testing by others [66,67].

The primary study strength is the mixed methods approach, which considered both quantitative and qualitative findings. To our knowledge, this is the second mixed methods publication on reproductive decision-making related to *FMR1* screening; the one prior report studied women with a family history of FXS [65]. As our interview and structured questionnaire data were consistent, it lends credibility to the findings. An additional strength is the clear clinical phenotype, thus the findings represent the experience of women with DOR without a family history of FXS.

Implications for clinical practice and/or policy

As more women without a FXS family history undergo this genetic carrier testing, it is a critical responsibility of the physician and the genetic counselor to provide accurate and objective information about the implications, advantages, disadvantages and consequences of this genetic testing and its results. Additionally, reproductive decisions before and after genetic counseling requires mutual understanding and co-operation between the clinician and the patient.

In terms of practice implications of our findings, women undergoing this testing need to have easy access to tailored educational materials, genetic consultation, and supportive environments before and after testing in order to understand the information the test could provide them. Without the benefit of the pretest genetic counseling and education materials offered in this study, women may not fully understand the implications of carrying the pre mutation. Recommendations on the content of *FMR1* pretest genetic counseling sessions have been published [25,68]. While specialists in reproductive medicine can provide a supportive environment to explain the meaning and implications of *FMR1* testing [69], it is important that patients have access to tailored educational materials and consultation with genetic counselors before and after testing as needed. Additional research is needed to determine what supplemental educational materials would be best suited to substitute for pretest counseling where pretest genetic counseling is not available.

As women with DOR continue to undergo *FMR1* testing in the future, it is important for clinicians and counselors to understand the reactions of these women with respect to genetic carrier testing.

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