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The impact of a family history of intellectual disability on fragile X carrier screening decisions

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I. Introduction

The objective of this study was to evaluate fragile X syndrome carrier screening decisions and trends in patients who report a family history of intellectual disability. Patients referred for genetic counseling undergo a detailed family history assessment that may reveal a history of intellectual disability of unknown etiology. Once a history of intellectual disability has been reported in a prenatal setting, genetic counselors must evaluate the risk to future offspring and offer relevant testing options. Fragile X syndrome is the most common inherited form of intellectual disability, affecting approximately 1/4000 males and 1/8000 females, regardless of ethnicity. An ACOG committee opinion (Number 691, March 2017, reaffirmed 2019) recommends fragile X syndrome carrier screening "for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant."

II. Methods

This study included patients seen for prenatal genetic counseling during 2018 who were referred for, or reported, a family history of intellectual disability in the female partner's family. Patients were excluded if they had previous carrier screening for fragile X syndrome. All patients in this cohort (n=1,407) received comprehensive genetic counseling during which the risk for intellectual disability and fragile X syndrome were assessed and the option of fragile X syndrome carrier screening was discussed. Decisions were documented as testing accepted (either performed or scheduled at physician direction), declined, or patient to follow-up with referring provider for further discussion. Patients were also evaluated based on whether the reason for referral was for intellectual disability, on the number of relatives affected, and on their degree of relationship to the pregnancy.

III. Results

Overall, 26.6% of patients who reported a family history of intellectual disability chose to pursue fragile X syndrome carrier screening, while 53.0% declined, and 20.4% wanted to follow-up with their referring physician (**Figure 1**). When a family history of intellectual disability was the reason for referral to genetic counseling, a significantly higher acceptance rate for carrier screening was noted (48.6%) (**Figure 2**) when compared to the acceptance rate when it was not the reason for referral (24.8%).

Figure 1: Fragile X Testing Decisions: History of ID

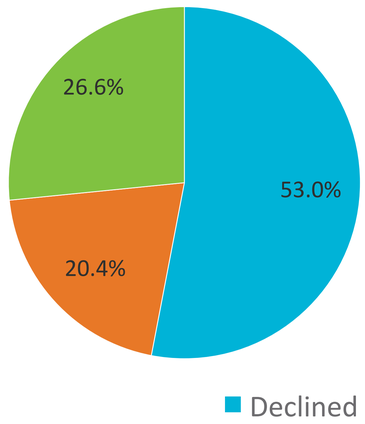
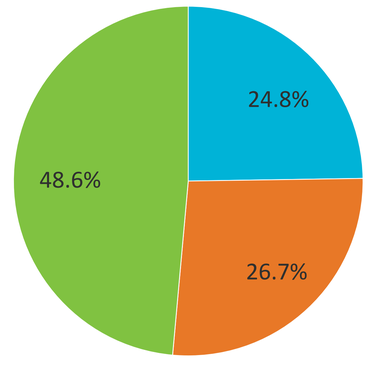


Figure 2: Fragile X Testing Decisions: ID as Referral Indication



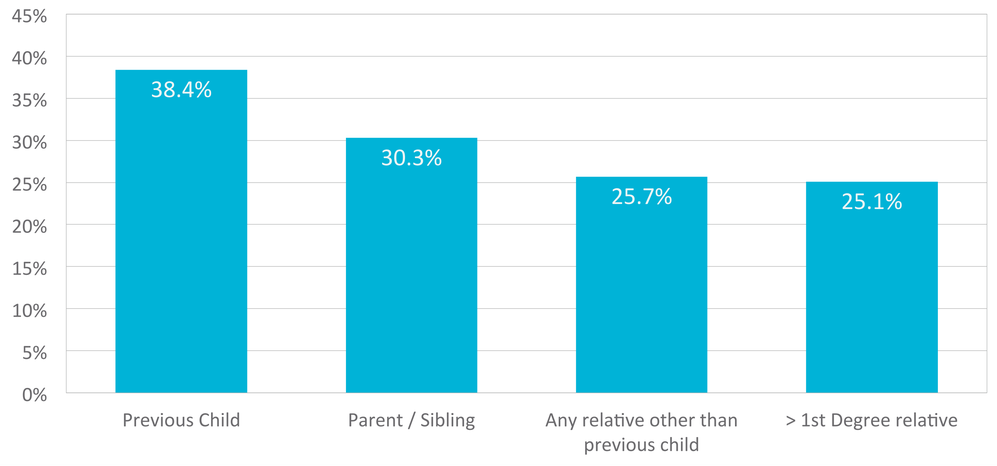
The vast majority of patients reported a single relative affected with intellectual disability. However, the percentage of patients who accepted carrier screening significantly increased between one and two affected relatives but did not increase further with greater than two relatives affected (**Table 1**).

Table 1: Fragile X Testing Decisions Based on Number of Affected Relatives

# Relatives	N	Accepted	Follow-up	Declined
1	1,262	25.5%	19.7%	54.8%
2	79	38.0%	27.8%	34.2%
3 or more	66	33.3%	27.3%	39.4%

When patients reported a previously affected child with their current or previous partner, 38.4% accepted carrier screening. This was significantly higher than the acceptance rate for patients with any affected relatives other than a previous child (25.7%) (p=<0.01). When comparing patients with an affected parent or sibling to those with non-first degree relative(s) affected, 30.3% of the former accepted carrier screening while 25.1% of the latter accepted. This was statistically significant (p=<0.001). Lastly, a direct comparison of decisions based on the type of first degree affected relatives, patients with an affected child accepted carrier screening 38.4% of the time versus 30.3% of the time when the affected relative was their parent or sibling (**Figure 3**). This difference was not statistically significant (p=<0.3).

Figure 3: Fragile X Testing Acceptance Rate Based on Affected Relative



IV. Conclusions

Obtaining a detailed family history during a comprehensive genetic counseling session allows for risk assessment related to the identified family history in the current or future pregnancy. Our study revealed that patients are more likely to pursue testing related to their family history when it is a significant personal concern or when the risks are higher due to the individuals affected. In the context of patients with a family history of intellectual disability in our study, these findings confirm the expectations.

Patients were the most likely to choose fragile X syndrome carrier screening when the family history of intellectual disability was the reason for referral. The next highest rate of acceptance was seen in patients with affected children, followed by patients with more than one affected relative, and lastly, patients with other 1st degree relatives affected. Our findings also suggest that a full discussion of risk and options during genetic counseling helps patients with a family history of intellectual disability make their most informed decision about fragile X syndrome carrier screening

V. References

Carrier screening for genetic conditions. Committee Opinion No. 691. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017; 129: e41-55.

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