# Fragile X carrier screening accompanied by genetic consultation has clinical utility in populations beyond those recommended by guidelines

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Disclosure: All authors are current or former employees of Myriad Genetics, Inc. and/or Myriad Women's Health

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## BACKGROUND

- Fragile X syndrome (FXS) is the most common inherited form of intellectual disability, with 1:151 women carrying an *FMR1* premutation that confers risk for FXS in offspring.
- ACMG and ACOG recommend *FMR1* carrier screening only in women with a family history (FHx) of FXS or related disorders, or for those undergoing fertility evaluation.
- Preconception and prenatal screening of all women for *FMR1* mutations is not yet recommended due to a perceived lack of clinical utility and the difficulties associated with adequately counseling large numbers of screened women.
- This study explored the clinical utility of *FMR1* carrier screening by analyzing actions, informed by post-test genetic consultation, among *FMR1* premutation carriers who do and do not meet criteria for screening.

## METHODS

- Cohort included women who:
  - Received expanded carrier screening (Sept. 2015-Dec. 2017, Myriad Women's Health)
  - Did not opt out of research involvement
  - Were *FMR1* premutation carriers
- Cohort was invited to answer a survey on their actions following receipt of screening results.

## RESULTS

- Providers recommended screening for 77% of patients, while 23% of patients requested screening (Table 1).
- Approximately 80% of screening occurred in those without a FHx, and approximately 50% occurred in those not undergoing fertility evaluation.
- Almost all patients received post-test genetic consultation (Table 1).

## RESULTS (CONT.)

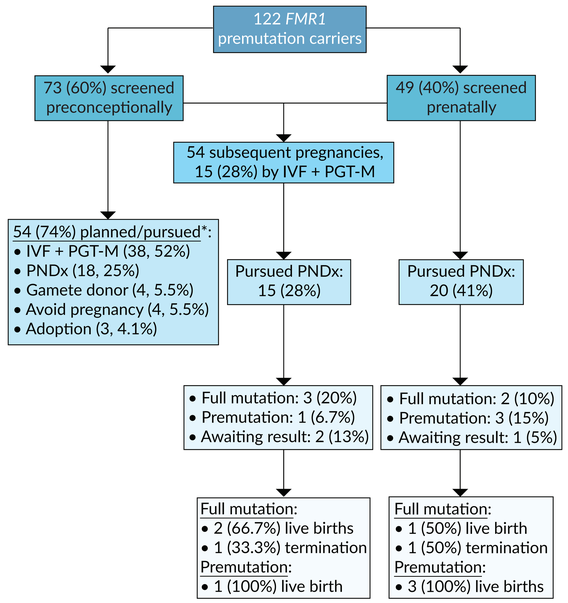
- When *FMR1* premutation carriers were screened preconceptionally, most (74%) pursued risk-reducing actions (Figure 1).
- When *FMR1* premutation carriers were screened prenatally, nearly half (41%) pursued prenatal diagnosis (Figure 1).
- More than one-quarter (28%) of subsequent pregnancies were achieved by IVF with PGT-M (Figure 1).

***Table 1. Screening Delivery Characteristics***

| | Total N (%) | Screened Pre-conceptionally N (%) | Screened Prenatally N (%) |
|---|---|---|---|
| Total Screened | 122 (100) | 73 (100) | 49 (100) |
| ***Instigation of Screening*** | | | |
| Provider-recommended | 94 (77) | 55 (75) | 39 (80) |
| Met screening criteria | 63 (67) | 51 (93)* | 12 (31)* |
| Did not meet criteria | 31 (33) | 4 (7.3) | 27 (69) |
| Patient request | 28 (23) | 18 (25) | 10 (20) |
| Met screening criteria | 14 (50) | 11 (61) | 3 (30) |
| Did not meet criteria | 14 (50) | 7 (39) | 7 (70) |
| ***Reason(s) for Screening*** | | | |
| Part of routine workup | 37 (30) | 8 (11) | 29 (59) |
| Part of fertility workup | 59 (48) | 52 (71)* | 7 (14)* |
| Ethnicity, female partner | 16 (13) | 9 (12) | 7 (14) |
| Ethnicity, male partner | 10 (8.2) | 4 (5.5) | 6 (12) |
| FHx, female partner | 26 (21) | 17 (23) | 9 (18) |
| FHx, male partner | 4 (3.3) | 4 (5.5) | 0 |
| Unknown FHx, either | 3 (2.5) | 1 (1.4) | 2 (4.1) |
| ***Post-test Genetic Consultation*** | | | |
| Yes, testing lab† GC | 71 (58) | 46 (63) | 25 (51) |
| Yes, other GC | 61 (50) | 28 (38) | 33 (67) |
| Yes, other provider | 66 (54) | 43 (59) | 23 (47) |
| None, but considering | 2 (1.6) | 1 (1.4) | 1 (2.0) |
| None, not considering | 0 | 0 | 0 |

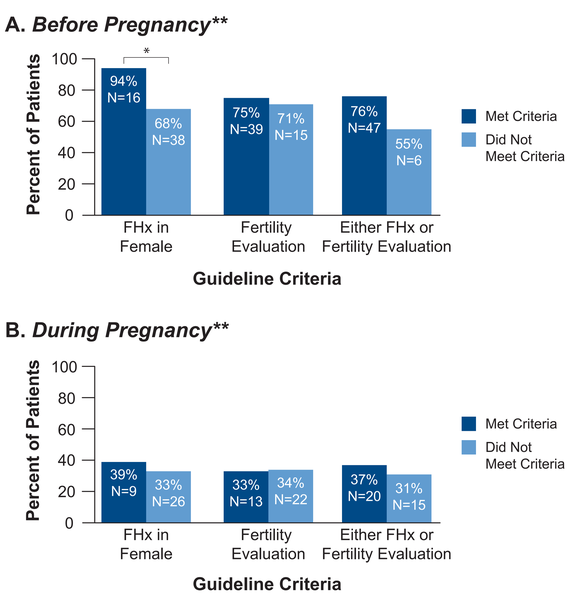
*Significant difference between those screened preconceptionally and those screened prenatally ($p<0.05$). †Myriad Women's Health; FHx, family history; GC, genetic counselor

***Figure 1. Risk-Reducing Actions Among Premutation Carriers.***




*Total N greater than 100% since it was possible to select >1 option. PGT-M, Pre-implantation genetic diagnosis for monogenic conditions; IVF, *in vitro* fertilization; PNDx, prenatal diagnosis.

***Figure 2. Impact of Screening Criteria on Risk-Reducing Actions.***




*Significant difference ($p<0.05$); **Risk-reducing actions before pregnancy: IVF+PGT-M, PNDx, donor gamete, avoidance of pregnancy, or adoption. Risk-reducing measure during pregnancy: PNDx; FHx, family history.

- For *FMR1* premutation carriers screened preconceptionally, FHx of FXS increased the likelihood of pursuing risk-reducing actions, but undergoing fertility evaluation did not (Figure 2).
- Pregnant *FMR1* premutation carriers pursued PNDx 41% of the time (Figure 1). FHx and fertility evaluation had no significant effect on PNDx (Figure 2).

## CONCLUSIONS

- Providers recommend, and patients desire, FXS carrier screening regardless of whether the patient meets current screening criteria.
- Patients who do not meet screening criteria take action to avert an affected pregnancy to nearly the same extent as those who do meet criteria.
- Nearly all patients made reproductive and pregnancy management decisions informed by genetic consultation.
- These results support FXS carrier screening for all women who are pregnant or considering pregnancy.

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