

TRENDS IN REPRODUCTIVE MALE PARTNER TESTING WHEN FEMALE
PATIENT IS IDENTIFIED TO BE A GENETIC DISEASE CARRIER

By

LAURIE M. SIMONE

A thesis submitted to the

School of Graduate Studies

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Master of Science

Graduate Program in Microbiology and Molecular Genetics

Written under the direction of

Elena Ashkinadze

And approved by

New Brunswick, New Jersey

May 2019

ABSTRACT OF THE THESIS

Trends in Reproductive Male Partner Testing When Female Patient is Identified to be a
Genetic Disease Carrier

By LAURIE M. SIMONE

Thesis Director:

Elena Ashkinadze

Expanded carrier screening (ECS) is a pan-ethnic blood test that identifies couples at risk for having a child with a rare genetic condition. Our aim was to quantify carrier testing uptake rates for male partners of an individual found to be a carrier for an autosomal recessive condition as well as potential barriers to test uptake rates. This was a retrospective chart review of female patients who were found to be carriers through expanded carrier screening panels, which determined how often their male partner chose testing, reasons for declining and type of methodology chosen for their screening. Seventy-seven percent of males had testing. We identified that the most significant barrier to male partner testing is female patients not following up on her carrier screening results; therefore, the partner was not offered testing. When male partners were provided options for testing, the most reported reason for declining is the belief it would have no impact on pregnancy management. A carrier couple rate of 8.3% was identified.

Keywords: expanded carrier screening, male partner testing, carrier couple

Acknowledgements

Thank you to Julia Lin and Sarah Trackman for assisting in the data abstraction process of this study.

Many thanks to Dr. Gary Heiman for assisting with the statistical analysis and my thesis committee (Elena Ashkinadze, Shama Khan, Molly Ciarlariello) for their constructive feedback throughout my research and this manuscript.

Lastly, thank you to my program director, Jessica Joines, for her overall support.

Table of Contents

Abstract.....	ii
Acknowledgements.....	iii
Introduction.....	1
Material and Methods.....	4
Results.....	6
Discussion.....	11

Introduction

The purpose of carrier screening is to identify women who are carriers for X-linked recessive disorders or couples at risk for having a child with an autosomal recessive genetic condition. While these individuals usually do not have a family history of a particular genetic disorder, they may still carry mutation(s) that could be transmitted to their offspring. On average, a healthy person is expected to be a carrier of one to two recessive lethal pathogenic variants (Gao et al., 2015). As part of preconception and prenatal care, individuals are offered carrier screening to determine if they are a carrier for a recessive condition. If women are found to be a carrier for an X-linked condition, they are counseled appropriately. If they are found to be a carrier for an autosomal recessive condition, carrier testing is facilitated for their partner. In some cases, concurrent partner testing is arranged from the onset. However, in many cases, the female is offered carrier screening first and if she screens negative, the risk for fetal disease is presumed to be low. The disorders included on these panels can vary by laboratory and often include disorders that are likely to impact decisions surrounding reproduction (American College of Medical Genetics, 2013).

The conditions that are commonly included on these carrier screens are based on recommendations established by the American Congress of Obstetricians and Gynecologists (ACOG) and the College of Medical Genetics and Genomics (ACMG) (American College of Medical Genetics, 2013). Most carrier screen panels do not include adult-onset disorders, such as hereditary hemochromatosis or syndromes in which there is dominant inheritance. As technology has improved and cost of carrier screening has continued to decrease, expanded carrier screening panels have become a viable option

compared to ethnicity-based screening with the ability to evaluate hundreds of variants associated with genetic disease (Nazareth et al., 2015). Historically, carrier screening was based on self-reported ethnicity or family history. Offering testing by ethnicity has proven to be increasingly challenging due to the rise in the number of individuals reporting mixed racial ancestry, patient preferences against the use of racial categorization in medicine and the possibility of unknown ancestry (Lazarin et al., 2013). Discrepancies have been reported between a person's self-reported ethnicity and genetic ancestry, indicating that self-reported ethnicity is not a reliable tool for clinical decision-making (Shraga et al., 2017). Given the increased ethnic heterogeneity of our population, there has been a shift from ethnicity-based carrier screening to the expanded carrier screening (ECS) model, allowing access to screening for multiple genetic conditions regardless of self-reported ethnicity. Because of the number of conditions listed on current ECS panels, it is expected that 20-40% of individuals screened will be a carrier for at least 1 condition (Lazarin et al., 2013).

In addition, carrier screening is performed using methodologies that vary in respective detection rates. ECS is performed by genotyping, sequencing, deletion/duplication analysis or a combination of all methodologies. However, sequencing can identify more pathogenic variants than genotyping method alone, allowing for the identification of more carriers and couples at risk for having a child with a genetic condition (Bell et al., 2011). Genotyping can help reduce the risk of having an affected child but does not eliminate risk (Lazarin et al., 2013). While sequencing does not eliminate the risk either, risk reduction is more significant compared to genotyping.

However, genotyping panels reduce the chance of identifying variants of unclear significance.

Identifying carrier couples has benefits. Knowing a fetus is affected by a recessive condition could impact management of the pregnancy and if possible, result in early intervention in the newborn period (Nazareth et al., 2015). It can also allow for resource identification and lead to familial testing cascades, allowing for identification of other at-risk individuals. Despite the benefits, some patients decline carrier screening when offered. While the rate of declining carrier screening is unknown, reasons that women decline carrier screening include lack of interest, no family history, and concerns about privacy or discrimination (Gilmore et al., 2017; Propst et al., 2018). Most studies have focused on why women decline carrier screening, but little is known about how the male partner of a woman who is a carrier perceives the results and the barriers that may exist for test up-take rates. There are general barriers to screening that include lack of awareness of personal risk, lack of knowledge of family medical history, and lack of knowledge of genetic services. There are also healthcare professional barriers including inadequate coordination of referral, lack of knowledge of patient's risk factors, and lack of obtaining accurate family medical history (Delikurt et al., 2015). Personal and financial barriers also exist. For example, a pregnant patient may receive coverage during her pregnancy such as Medicaid or Charity Care, but her partner may remain uninsured. Couples were more likely to pursue testing if they had a 'child wish', that is, an idea of how they hope their child to be; have a positive attitude towards screening; and/or experience the choice to participate as easy. Those that consider themselves to be areligious were more prone to test as well (Voorwinden et al., 2017). Factors related

specifically to male partner decline of testing include patient-partner relationship, family involvement, socioeconomic status as well as past pregnancy history (Pergament & Pergament, 2012). In addition, it is unclear if the availability of ECS has affected the rate of declining. Current studies have not explored male partner uptake of expanded carrier screening and the specific barriers encountered by these individuals. Considering the purpose of ECS is to identify carrier couples, partner screening is of great importance.

Here, we present data regarding carrier testing uptake rates for male partners of an individual found to be a carrier for an autosomal recessive condition. In addition, we will identify potential barriers to male test uptake rates in a busy Maternal Fetal Medicine practice. We conducted a retrospective chart review of female patients who were found to be carriers through expanded carrier screening panels and evaluated whether their male partner pursued testing, barriers to test up-take rates, and the methodology used (genotyping or sequencing) for their testing.

Materials and Methods

Subjects

A retrospective cohort study was conducted of records from January 1, 2017 to March 1, 2018 at Rutgers-Robert Wood Johnson Medical School in New Brunswick, New Jersey. Women who were identified as carriers of a condition through expanded carrier screening were included in this study. Charts of women and men less than 18 years old were excluded. Women that were identified as carriers for X-linked conditions like Fragile X syndrome were excluded (n=19). The number of individuals who met eligibility criteria were 513 female patients. All data was de-identified. The Rutgers University Institutional Review Board (IRB) approved this study.

Male Partner Testing

When male partners were offered testing, they were provided options for genotyping, sequencing and/or complete blood count/hemoglobin electrophoresis, when appropriate. When the female patient was identified to be a carrier, male partner testing was either targeted to the specific condition or the partner had expanded carrier screening. The rationale for selecting the laboratory to perform the testing was dependent on methodology type, insurance coverage and overall partner's willingness to accept any potential out-of-pocket costs.

Data Abstraction

Subjects were initially identified from the genetic counseling patient logs which tabulate each patient seen and the indication for the visit. Once the patients were identified, their consultation summary from that visit was reviewed. The consultation notes for all patients seen for genetic counseling and found to be carriers on expanded carrier screening were obtained from the Centricity electronic medical record. If it was determined that the female proband was a carrier for an autosomal recessive condition and male partner carrier screening was indicated, the patient was included in the study data set. For those who met inclusion criteria, we abstracted the following data: patient and male partner's demographics (age, ethnicity), insurance type (commercial, Medicaid, uninsured), indication for referral, patient's and partner's carrier status, methodology of testing for partner (genotyping, sequencing, other). For partners who declined testing, reason for declining was also determined from consultation notes. Any consult letters and genetic test results available through their records were thoroughly reviewed.

Data Analysis

Descriptive statistics (frequencies of categorical responses and means of continuous variables) were calculated. In the case of missing data, a mean score was calculated based on responses provided. We quantified the number of patients and partners that were identified to be carriers. We then determined how often carrier screening was conducted by genotyping versus sequencing and rationale for choosing one methodology versus the other. We also tried to determine from the genetic counseling consultation summary the reason(s) for partner decline of testing. Statistics were performed using STATA with statistical significance set at $P < .05$. When comparing partners who pursued testing to those who did not, subjects with missing variables for age and insurance type were removed. Partners that were not able to be offered testing because they were unavailable (ex: sperm donor or unknown partner) were not included in the analysis, due to the inability to determine potential outcome. A total of 476 subjects were included in the logistic regression. We used predictive modeling for the logistic regression to best determine the outcome of partners deciding to get tested.

Results

Demographics

A total of 513 female patients were found to be carriers of a genetic variant through expanded carrier screening during January 1, 2017 to March 1, 2018. The mean age of female patients that met criteria was 32.6 years (range 19 years to 45 years) and the mean reported age for male partners was 34.7 years (range 19 years to 62 years). The majority of subjects identified as white in both female patients and male partners (56% and 73%,

respectively). Table 1 reflects the ethnicities of patients as well as the reported ethnicities of partners. The female's insurance type was obtained with 450 (88%) of patients having commercial insurance, 56 (11%) having Medicaid/Charity Care, and 6 (1%) patients having no insurance. One patient had unknown insurance coverage. A total of 7 patients were not pregnant at the time of consult.

Female Patient's Ethnicity	% of Total	Male Partner's Ethnicity	% of Total
NH - White	56%	NH - White	73%
NH - Asian	19%	NH - Asian	9%
Hispanic	13%	Hispanic	9%
NH - Black	10%	NH - Black	6%
Multiple	1%	Multiple	2%
Other	1%	Unknown	1%
Grand Total	100%	Grand Total	100%

Table 1. Patient and Partner's Ethnicities. Patient and partner's ethnicities are reflected by number of individuals identified per group and the overall percentage of individuals that fell into the ethnic group out of the total number of individuals (513) NH= Non-Hispanic.

Female Patient testing

After patients were identified as carriers, they were informed of their results by phone and scheduled for face-to-face genetic counseling and asked to bring their partner. During that session, the female patient was counseled regarding the clinical features associated with the specific condition(s) for which she was found to be a carrier. She and her partner, if present, were also counseled on autosomal recessive inheritance, the chance for partner to be a carrier, strategy of carrier testing for the partner and rationale, and the option of prenatal diagnosis in at risk couples. The patient was provided a copy of her carrier screening result and encouraged to share the result with her family members. Twenty-three percent of patients were identified to be carriers of more than 1 condition.

Male Partner testing

The male subject was then offered carrier screening for the disease(s) in question. The benefits and limitations of the genotyping assay as compared to the sequencing assay were reviewed. Carrier testing for the male partner was offered.

A total of 394 (77%) male partners went on for testing. Out of the 394 partners who pursued testing, 216 (55%) opted for testing through genotyping, 154 (39%) sequencing and 24 (6%) CBC/hemoglobin electrophoresis. Figure 1 shows an overall breakdown of decisions made, dependent on if partner obtained or declined testing. Four males were found to have a variant of uncertain significance (VUS) by sequencing for the specific condition in question. This results in a VUS rate of 2.6% (4/154).

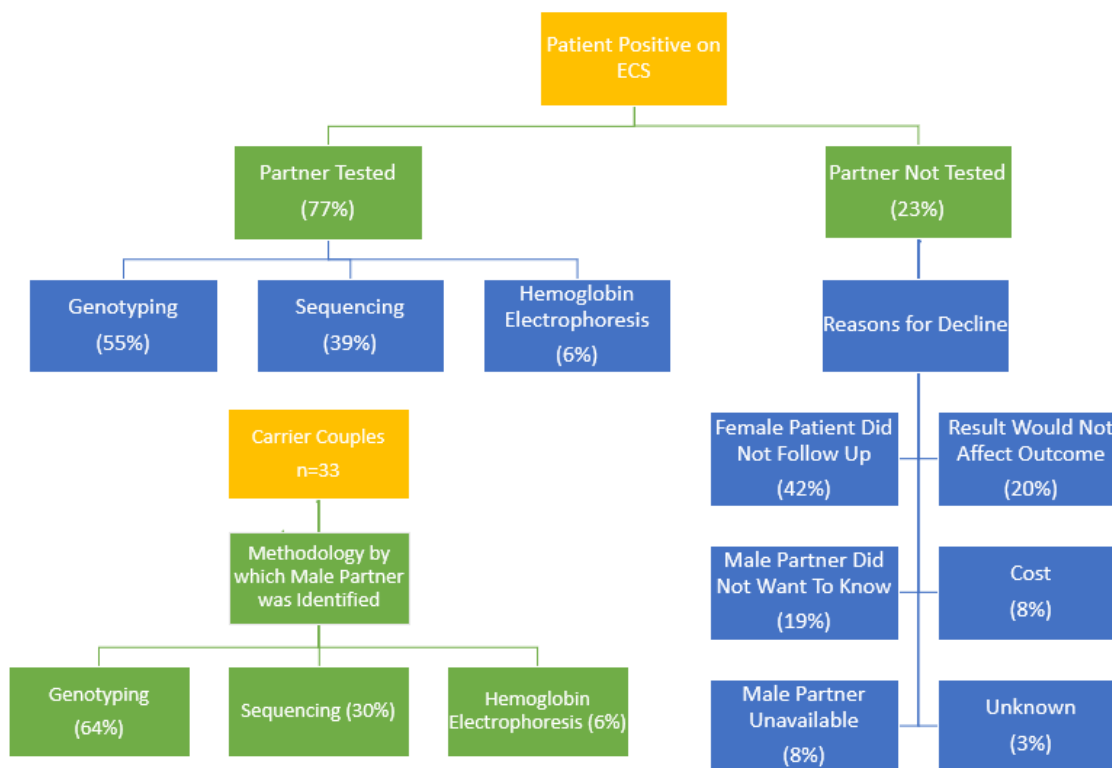


Figure 1. Decision tree demonstrating male partner decisions regarding testing, testing methodologies, reasons for declining testing and partner testing methodology of identified carrier couples.

A total of 119 (23%) partners did not pursue any type of testing. Reasons for male partner decline were identified in consultation summary. The most common reason male partners did not have carrier testing was due to the female patient not following up on her carrier screen results, encompassing 42% of these partners (Figure 2). That is, patients did not come for their scheduled follow-up appointments when they were identified as carriers and therefore, testing could not be offered/coordinated for their partner. The most reported reason for declining in males who were offered testing was that the couple felt that the result would not impact pregnancy outcome, (20% or 24/119).

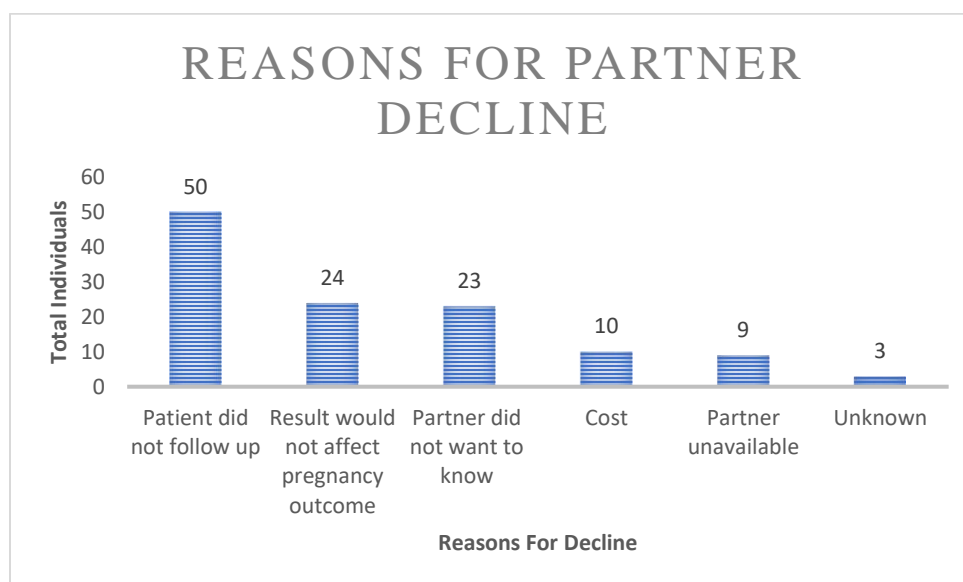


Figure 2. Reasons identified on chart notes for partner decline of carrier testing. Total: 119

Predictive Model

Patient and male partner age was not found to affect the decision to have partner testing. Compared to whites, Hispanic males were 1.92 (OR) less likely to pursue testing ($p=0.05$; 95% CI: 0.99 – 3.73). Patient insurance type was found to be an indicator for whether their male partner pursued testing. Compared to commercial insurance, females with Medicaid or Charity Care were 2.41 (OR) less likely to have their partner tested ($P =$

0.01). Overall, our predictive model only explains about 3.5% of the decision to have the partner tested (Pseudo $R^2 = 0.035$). This indicates that all combined factors analyzed (patient and male partner's age, ethnicities, or female's insurance type) were poor indicators of whether partner would pursue testing.

Carrier couples

Condition	Carrier Couples Identified
Achromatopsia	1
Alkaptonuria*	1
Biotinidase deficiency	2
Cystic Fibrosis*	4
Congenital Disorder of Glycosylation	1
Familial Dysautonomia	1
Familial Mediterranean Fever	4
Fumarase Deficiency*	1
Galactosemia	2
Gaucher Disease	2
GJB2-Related Non-Syndromic HL	2
Hemochromatosis	4
Non-Classic CAH	1
Phenylketonuria	1
POMT2-related CMD	1
Primary congenital glaucoma	1
Sickle beta thalassemia	1
Sickle Cell Disease	3
Stargardt Disease	1
Tay-Sachs Syndrome*	1
Total	33

Table 2. Carrier couple types identified that are at risk of having an affected child. HL = hearing loss, CAH = congenital adrenal hyperplasia, CMD = congenital muscular dystrophy. Asterisks indicate 2 couples identified as carriers of more than one condition.

We identified various couples in which both patient and partner were found to be heterozygous carriers for the same condition. Partners who were identified as having a

VUS in the condition in question were excluded (n=4). The “carrier couple” frequency overall was 10.2% (40/394). Five couples were found to be mutual carriers of silent alpha thalassemia and 2 couples were carriers of alpha thalassemia trans (a/-; a/-); this poses no risk to their offspring for disease. Thus, these were excluded. The carrier couple frequency for couples at risk to have an affected child was 8.3% (33/394). The conditions most identified in carrier couples were Familial Mediterranean Fever and Hemochromatosis as seen in *Table 2*. Hemochromatosis is typically not included on carrier screen panels because of the adult-onset nature of the condition. However, some patients had a panel that included hemochromatosis. If excluded, the carrier couple frequency is 7.3%. Two couples were found to be carriers of the same two conditions (Cystic Fibrosis and Alkaptonuria; Tay-Sachs syndrome and Fumarase Deficiency) and were counseled on the 25% risk of each condition for their offspring. In the majority of carrier couples identified, the male partner had his testing completed by genotyping (64%) (Figure 1).

Discussion

The objective of this study was to determine trends in reproductive male partner testing. Our study found that 77% of males went on to have carrier testing, after their female partner was identified to be a carrier. However, 23% did not pursue testing, despite their reproductive partner being a carrier for a genetic disease.

Other studies on expanded carrier screening reported lower uptake rates even when the subjects had health insurance. Although a smaller study, Rothwell et al. (2017) reported 8 partners not undergoing testing when 17 patients had positive carrier results. Partners who declined testing in this study were described as unavailable or unwilling to

be tested, resulting in an uptake rate of 52.9%. We believe the higher uptake rate in our study may be due to our center's protocol for arranging post-test counseling appointments and drawing the partner's blood on the day of the follow-up visit. In addition, the female patient, when found to be a carrier, is informed via telephone by a genetic counselor. Then, the patient and her partner were asked to come in person for face to face genetic counseling. During the session, the condition(s) were explained again in detail which we would speculate increases patient comprehension. In addition, even if the male partner did not have insurance coverage, we were able to offer free or reduced fee testing in many cases. All these factors are likely to contribute to a higher male test uptake rate. In cases when the couple indicated that they would not consider termination of pregnancy if the fetus was affected, they were also counseled regarding the potential benefits, in some conditions, for neonatal/pediatric intervention. The carrier screening was explained as a possible "reverse newborn screen." The purpose of newborn screening was discussed, and it was explained that expanded carrier screening may identify many of those conditions but potentially even more than what is available on the newborn screen.

Our data also suggests that there are no clear differences in age between male partners who chose testing as compared to those who declined. Male partners were, on average, older than the patients. In general, men are older than women within a relationship in the United States (NW, Washington, & Inquiries, 2012). We did find that Hispanic males were less likely to pursue testing compared to white males; however, it is unclear if this is related to other factors, such as socioeconomic status.

We observed an unexpectedly high rate of carrier couples with a rate of 8.3%. In contrast to our observations, other studies have reported lower rates of carrier couples. A

study conducted at a Jewish genetics center using a panel of 84 disorders and Fragile X had a carrier couple rate of 4.3% (Arjunan et al., 2016). Another study reported a rate of 1.2% and 3.1% for the two ECS genotyping panels used (Bristow et al., 2019). The larger panel used in this study included screening for 307 genetic diseases. The panels offered at our clinic varied in number of conditions and variants screened, with most panels including 100 – 150 different conditions. Our high rate may be explained by the differences in methodology as 30% carrier couples identified had sequence-based testing for the male partner. Previous studies have reported that 25% of mutations found on sequencing-based screening panels would not have been detected on genotyping-based panels (Nazareth et al., 2015). Sequencing would detect more carriers than genotyping, allowing a higher detection of carrier couples.

Our findings demonstrate that genotyping was the most common methodology used for male partner testing. This is likely a decision related to cost of testing, as often genotyping ECS panels are less expensive than sequencing panels and more readily available. However, sequencing has a higher sensitivity, detecting a larger number of pathogenic variants than genotyping (Bell et al., 2011). The high sensitivity of sequencing can result in the detection of variants that have not been identified as pathogenic or benign and are considered variants of uncertain significance. We did identify a VUS rate of 2.6% in partners that had sequencing. However, some sequencing laboratories do not report variants of uncertain significance and therefore, this rate may be even higher if carrier screening labs report on all variants. This highlights the challenges of using a sequencing-based platform. In our study, four couples were counseled that the female is a carrier for a known pathogenic mutation, but the partner is

a carrier for a VUS. Predicting phenotype for a theoretical compound heterozygote offspring was not possible. Thus, this creates challenging counseling dilemmas and potentially increases anxiety to the couple. Adequate pre- and post-test counseling is essential to help couples understand the residual risk that remains with this genotyping as well as the potential risk for variants of uncertain significance for sequence-based tests (Wienke et al., 2014). Both testing methodologies help couples obtain valuable information for family planning.

“Results will not affect pregnancy outcome” was the most common reason why male partners declined testing. Despite couples expressing that carrier results would not affect pregnancy outcomes, knowing their carrier status has benefits. This can help couples prepare for potential birth complications and may help the child seek necessary evaluations (Nazareth et al., 2015). Knowing that this is a reason why partners may decline testing may help guide the conversation towards the benefits of potential neonatal or pediatric intervention. Reasons why partners declined in this study differed from reasons identified for female patients in other studies. Other studies often reported lack of time or interest as the most common reasons; some reported not wanting to know and worry (Gilmore et al., 2017).

We found that cost was a barrier for 8% of partners who declined testing. The female patient’s insurance type was also a significant indicator for partners declining testing, with those with Medicaid or Charity Care twice as likely to decline partner testing compared to patients with private insurance. This may be due to their partners not having insurance. In male partners that were underinsured, we were able to offer free or

reduced fee testing in many cases; yet, this was still a reported barrier for some males. Insurance type is our only potential indicator of socioeconomic status.

Patient follow-up was identified as a major barrier to testing partners. This clinic informs patients of positive carrier test results by phone. A total of 50 (9.7%) female patients who were found positive on expanded carrier screening did not follow up with a post-test counseling visit. Patients may have failed to follow-up due to time constraints, may have believed the condition they were found to be carriers for is not a severe phenotype, or misunderstood the significance of the test result. It is also possible that the male partner was unavailable or disinterested in getting tested and therefore, the patient did not find it necessary to complete post-test counseling. Because of this, we were unable to truly assess whether their partners would have accepted or declined.

Study Limitations

This was a qualitative retrospective research study at a university-based maternal fetal medicine practice. Most subjects were pregnant so there were time limitations for pregnancy outcome decisions. Education levels and income were not analyzed and may have had an impact on partners opting for testing. This study did not collect information on socioeconomic status or insurance type for the partner, which can further clarify cost as a barrier. Socioeconomic factors that may affect partner testing may include education level and net income. In our study, we did not have full access to all male patients as some males were unavailable or their female partners did not follow-up to discuss their own results. We do not truly know if the males who were not offered testing directly would have pursued carrier screening. Some male partners had concurrent testing with

the female patient, and these were often genotype-based tests. This may have led to higher rates of genotyping.

Research Recommendations

Future research should focus on why some carriers do not follow-up on their own results and do not pursue partner testing. Other studies may also identify changes in partner uptake rates over time, as carrier screening methodologies evolve and cost of testing decreases. An analysis of patient follow-up in other centers may be beneficial to determine if this is a common barrier for partner testing. In addition, studies are needed to evaluate the challenges couples face when variants of uncertain significance are identified and the phenotype in the fetus cannot be accurately predicted. It is important to study whether these patients pursue prenatal diagnosis and their ultimate pregnancy decisions, when faced with uncertainty.

Conclusion

In summary, the high carrier couple rate supports the relevance of expanded carrier screening to identify couples at risk to have an affected child. The relatively high male uptake rate, after female carrier status is established, illustrates that expanded carrier screening can be implemented in the general population. An analysis of partner uptake rates with age did not show an association; however, an association between insurance type and partner decline was observed. The reasons for decline encompassed all groups. The VUS rates emphasize the importance of adequate pre- and post-test counseling on limitations of sequence-based tests. Expanded carrier screening is dependent on results from both parents. Thus, it is prudent to explore prior to testing the female whether her

male partner will be available and willing to proceed with carrier testing, if her carrier status is established.

References

- American College of Medical Genetics. (2013). ACMG position statement on prenatal/preconception expanded carrier screening. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 15(6), 482–483. <https://doi.org/10.1038/gim.2013.47>
- Arjunan, A., Litwack, K., Collins, N., & Charrow, J. (2016). Carrier screening in the era of expanding genetic technology. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 18(12), 1214–1217. <https://doi.org/10.1038/gim.2016.30>
- Bell, C. J., Dinwiddie, D. L., Miller, N. A., Hateley, S. L., Ganusova, E. E., Mudge, J., ... Kingsmore, S. F. (2011). Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Science Translational Medicine*, 3(65), 65ra4. <https://doi.org/10.1126/scitranslmed.3001756>
- Bristow, S. L., Morris, J. M., Peyser, A., Gamma, A., Singer, T., Mullin, C., ... Hershlag, A. (2019). Choosing an expanded carrier screening panel: comparing two panels at a single fertility centre. *Reproductive Biomedicine Online*, 38(2), 225–232. <https://doi.org/10.1016/j.rbmo.2018.11.018>
- Delikurt, T., Williamson, G. R., Anastasiadou, V., & Skirton, H. (2015). A systematic review of factors that act as barriers to patient referral to genetic services. *European Journal of Human Genetics*, 23(6), 739–745. <https://doi.org/10.1038/ejhg.2014.180>
- Gao, Z., Waggoner, D., Stephens, M., Ober, C., & Przeworski, M. (2015). An estimate of the average number of recessive lethal mutations carried by humans. *Genetics*, 199(4), 1243–1254. <https://doi.org/10.1534/genetics.114.173351>
- Gilmore, M. J., Schneider, J., Davis, J. V., Kauffman, T. L., Leo, M. C., Bergen, K., ... Goddard, K. A. B. (2017). Reasons for Declining Preconception Expanded Carrier Screening Using Genome Sequencing. *Journal of Genetic Counseling*, 26(5), 971–979. <https://doi.org/10.1007/s10897-017-0074-y>
- Lazarin, G. A., Haque, I. S., Nazareth, S., Iori, K., Patterson, A. S., Jacobson, J. L., ... Srinivasan, B. S. (2013). An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 15(3), 178–186. <https://doi.org/10.1038/gim.2012.114>

- Nazareth, S. B., Lizarin, G. A., & Goldberg, J. D. (2015). Changing trends in carrier screening for genetic disease in the United States. *Prenatal Diagnosis*, 35(10), 931–935. <https://doi.org/10.1002/pd.4647>
- NW, 1615 L. St, Washington, S. 800, & Inquiries, D. 20036 U.-419-4300 | M.-419-4349 | F.-419-4372 | M. (2012, February 16). The Rise of Intermarriage | Pew Research Center. Retrieved February 24, 2019, from <http://www.pewsocialtrends.org/2012/02/16/the-rise-of-intermarriage/>
- Pergament, E., & Pergament, D. (2012). Reproductive decisions after fetal genetic counselling. *Best Practice & Research. Clinical Obstetrics & Gynaecology*, 26(5), 517–529. <https://doi.org/10.1016/j.bpobgyn.2012.04.001>
- Propst, L., Connor, G., Hinton, M., Poorvu, T., & Dungan, J. (2018). Pregnant Women's Perspectives on Expanded Carrier Screening. *Journal of Genetic Counseling*. <https://doi.org/10.1007/s10897-018-0232-x>
- Rothwell, E., Johnson, E., Mathiesen, A., Golden, K., Metcalf, A., Rose, N. C., & Botkin, J. R. (2017). Experiences among Women with Positive Prenatal Expanded Carrier Screening Results. *Journal of Genetic Counseling*, 26(4), 690–696. <https://doi.org/10.1007/s10897-016-0037-8>
- Shraga, R., Yarnall, S., Elango, S., Manoharan, A., Rodriguez, S. A., Bristow, S. L., ... Puig, O. (2017). Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. *BMC Genetics*, 18(1), 99. <https://doi.org/10.1186/s12863-017-0570-y>
- Voorwinden, J. S., Buitenhuis, A. H., Birnie, E., Lucassen, A. M., Verkerk, M. A., van Langen, I. M., ... Ranchor, A. V. (2017). Expanded carrier screening: what determines intended participation and can this be influenced by message framing and narrative information? *European Journal of Human Genetics: EJHG*, 25(7), 793–800. <https://doi.org/10.1038/ejhg.2017.74>
- Wienke, S., Brown, K., Farmer, M., & Strange, C. (2014). Expanded carrier screening panels-does bigger mean better? *Journal of Community Genetics*, 5(2), 191–198. <https://doi.org/10.1007/s12687-013-0169-6>