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A Retrospective Chart Review Examining the Clinical Utility of Family Health History

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Abstract

Family health history (FHH) is a simple and cost-effective clinical tool widely used by genetic professionals. Although the value of FHH for assessing personal and familial health and reproductive risk within a prenatal population has been demonstrated in past studies, its utility within a genetic carrier screening population has not been evaluated. The purpose of this study was to examine the utility of FHH as a clinical screening tool and explore the general outcomes of full FHH evaluations within an expanded carrier screening (ECS) population. A retrospective chart review was conducted for 500 consults, which included 3-generation pedigrees, using data from the genetic testing company Recombine. Data from the consult letters were examined to assess the incidence of findings that met criteria for further action. Findings were assigned to 1 of 2 categories: requiring further follow-up, or requiring general risk counseling, which could include risk assessment and/or patient education. Analysis was done to examine the types of follow-up recommendations that were made and the topics discussed in general risk counseling. Of the 190 consults with negative carrier screening results, 117 (23.4% of the total consults) had additional indications in the family histories that warranted recommendations for further follow-up, general risk counseling, or both. The family history evaluations elicited cancer genetic counseling recommendations in 141 consults with either positive or negative carrier screening results, which comprised 28.2% of all consults (95% confidence interval of 3.94%). Autoimmune and psychiatric disorders were the most frequent topics requiring general risk counseling, occurring in 16.8% and 10.0% of all consults (95% confidence interval of 3.28% and 2.62%, respectively). These findings demonstrate the high clinical utility of FHH and validate its use in healthcare settings. FHH evaluations provide supplemental information to an individual or

couple's ECS results, allowing for more personalized health and reproductive risk assessments.

Introduction

Family health history (FHH) is an integral part of genetic counseling consultations. Collecting FHH in the form of a pedigree often serves as the initial step for a genetic evaluation (Bennett, 2012). The pedigree provides a graphic representation of medical-family information and biological relationships through standardized nomenclature established by the Pedigree Standardization Task Force of the National Society of Genetic Counselors (Bennett et al., 1995; Bennett et al., 2008). This allows for an easy and consistent method of recording and interpreting family health information. The family pedigree has long been recognized as a cost-effective risk assessment tool (Bennett, 2012). It can be used to identify at-risk individuals, establish patterns of inheritance, calculate disease risks, and distinguish genetic contributions from other risk factors (2012). One of its particular advantages is assisting in risk assessment for conditions without a known molecular cause or distinct Mendelian inheritance pattern (Brenda J Wilson et al., 2009)

The scope of a FHH evaluation is often dependent on the practice setting and patient population (ACOG, 2011). Each type of evaluation serves its own purpose and offers its own advantages. Directed family history evaluations utilize targeted questions for the purpose of assessing disease-risk; these types of directed evaluations are typically used in specialties such as cancer genetics, neurogenetics, and cardiovascular genetics to capture FHH information that is relevant to the condition being assessed (Blankstein & Foody, 2014; Lu et al., 2014; Rubinstein et al., 2011). Detailed family history evaluations tend to be broader in

scope and are more frequently used in preconception and prenatal care (Farahi & Zolotor, 2013). A number of professional health organizations, including the Centers for Disease Control and Prevention, U.S. Office of the Surgeon General, American Heart Association, American College of Obstetrics and Gynecology, and American Society of Clinical Oncology, endorse the use of thorough FHH as a risk assessment tool given its many benefits (ACOG, 2011; Lu et al., 2014; Tarini & McInerney, 2013; Wu et al., 2015).

Besides its effectiveness as a risk assessment tool, the utility of FHH as a clinical tool is evident by the array of other functions it serves. It is useful for making a diagnosis, guiding testing strategies, determining reproductive options, and informing decisions on medical management and surveillance (Bennett, 2012). Collecting FHH also presents opportunities for rapport building, patient education, and exploration of the patient's understanding of the condition or disease of interest (2012).

There are significant systemic, clinician, and patient-barriers to FHH that hinder its application in clinical practice (Wu et al., 2015). Systemic barriers include limited resources, including the time and availability of clinical personnel to obtain a thorough family history (2015). Clinician barriers include the availability of licensed and/or certified genetic professionals with the knowledge and skills to synthesize and interpret family history data for risk stratification (2015). Patient barriers pertain to the inherent limitations of patient-reported information (2015). A systematic review of the role of family history in risk assessment conducted by Wilson et al. found that the absence of disease in relatives is more often correctly reported than the presence of disease (Brenda J Wilson et al., 2009). This shows that patient-reported family history data has the potential to be inaccurate or incorrect.

Inadequate knowledge about FHH presents an additional barrier in the medically underserved population (Kaphingst et al., 2012).

FHH can be made more valuable when used in conjunction with genetic testing; FHH provides context for the interpretation of genetic testing results, and risk factors identified through FHH evaluation may prompt consideration of more extensive genetic evaluation and/or testing (Bennett, 2012). The type of genetic evaluation or testing is often specific to the practice setting.

In reproductive medicine, population-based carrier screening is an integral part of genetic testing and is gaining more widespread use as a screening tool (Yao & Goetzinger, 2016). Historically, the initial aims of genetic carrier screening focused on identifying carriers to prevent disease occurrence and reduce disease frequency in successive generations (Khoury, McCabe, & McCabe, 2003). In the 1970's, carrier screening focused on identifying carriers of Tay-Sachs disease within the Ashkenazi Jewish population (Beaudet, 2015). Due to historical and social factors that limited potential reproductive partners, there was a high incidence of Tay-Sachs within this population (Gross, Pletcher, & Monaghan, 2008). With the rapid progression of disease-causing genes being identified in other specific populations, ethnicity-based carrier screening panels were expanded to include additional diseases, such as β-thalassemia, sickle cell anemia, and cystic fibrosis (Beaudet, 2015). By the 2010's, many companies began to offer 'universal carrier screening,' as opposed to ethnicity-based screening for only the at-risk populations (2015). Screening panels went from testing more than 100 genes using SNP-microarray to applying next-generation sequencing to 437 target genes (2015). Genetic carrier screening has evolved to encompass autosomal recessive and x-linked disease causing genetic variants (2015). With the increasing awareness among genetic

carrier screening, the American College of Obstetricians and Gynecologists has endorsed the use of universal carrier screening in the prenatal and preconception setting (Romero, Rink, Biggio, & Saller, 2017). The recent modification was brought about by the growing uncertainty of a patient's entire ethnicity or background (2017). As healthcare providers and professional organizations push toward universal testing, the need for patient education about the testing received, and risk assessment of the testing results, will increase.

In the preconception and prenatal care setting, genetic carrier screening is often a standard recommendation and is an essential component of predicting risk for inherited genetic conditions (Edwards et al., 2015). In this setting, genetic carrier screening is typically used in conjunction with FHH to assess an individual's personal and reproductive risk (Farahi & Zolotor, 2013; Yao & Goetzinger, 2016). The aim of genetic carrier screening is to identify individuals who carry a disease-causing variant that places them at an increased risk for having offspring affected with that condition (Beaudet, 2015). This risk is particularly significant if the individual's partner is found to be a carrier of the same condition (2015). Genetic carrier screening enables at-risk couples to be informed of the genetic risks to their offspring and of the reproductive options available to them (Borry et al., 2011). Genetic carrier screening also provides couples with the opportunity to actively engage in managing their reproductive risks through preconception planning and the use of in vitro fertilization with pre-implantation genetic diagnosis (IVF with PGD) (Edwards et al., 2015). Through IVF with PGD, high-risk couples have the option to screen for specific genetic conditions prior to transfer of the embryo, greatly reducing their risk of an affected offspring (Antonios, 2012). Genetic carrier screening also allows for early detection of potentially affected

offspring, which may assist in the development of specific management protocols and lead to greater preparedness within families (Ross, Ross, Saal, David, & Anderson, 2013).

Genetic carrier screening and FHH are mutually informative tools for obtaining insight into reproductive risk. While several studies have looked into the utility of directed family history as a risk assessment tool for specific diseases, few have examined the overall utility of family history as a clinical tool. For the 2009 National Institute of Health State-of-the-Science conference, the Agency for Healthcare Research and Quality prepared a systematic review, which found a dearth of evidence to support the clinical utility of FHH (Tarini & McInerney, 2013). The purpose of this study was to examine the general outcomes of full family history evaluations in the context of post-expanded carrier screening genetic counseling sessions. Further goals of this study were to describe the type of information that can be elicited from a FHH evaluation and to evaluate the clinical utility of the information elicited.

Materials and Methods

This study is a retrospective chart review using Recombine's patient database. Recombine is a genetic testing company that provides expanded carrier screening (CarrierMap). The CarrierMap panel assesses an individual's carrier status for approximately 300 autosomal recessive and x-linked conditions (Appendix A). A randomly selected sample of consults from February 1, 2016 to February 29, 2016 was screened for eligibility into the study. A total of 500 consults meeting the inclusion criteria were obtained. The inclusion criteria included consults in which an individual or a couple received CarrierMap testing, and subsequently consented to a full family history evaluation. For the purpose of this study, a

full family history evaluation was defined as a three-generation pedigree in which family members were assessed for intellectual disabilities, learning disabilities, birth defects, blindness, deafness, muscle or skeletal disorders, blood disorders, infant deaths, infertility, recurrent pregnancy loss, consanguinity, and known genetic conditions. The consults were conducted by twenty-one licensed and/or certified genetic counselors with varying years of experience. Data was extracted from the consult letters, and coding was specified for the following variables: consult ID, genetic counselor conducting consult, couple or individual consult, reported gender, date of birth, ethnicity of each individual, indication for testing, carrier screening results, additional follow-up testing based on the carrier screening results, FHH findings such as those requiring recommendations for further follow-up or general risk counseling, and known genetic conditions in the family. For the analysis, FHH findings were assigned to one of two categories: requiring further follow-up, or requiring general risk counseling, which could include risk assessment and/or patient education. General risk counseling was defined as any discussion on reproductive or recurrence risk based on family history and available empiric data. Patient education does not generally include personalized risk information, and may be a part of the general risk counseling process, depending on the patient's knowledge and understanding of the condition being discussed. When a patient received education, information was discussed about the reported finding or condition, including clinical features and patterns of inheritance. Data was de-identified, and no identifiable information was stored. Because the data included private health information, it was maintained in a password-protected database. Once data extraction was completed, the original spreadsheet containing the health privacy information was destroyed.

Initial statistical analysis was performed by a statistician at Sarah Lawrence College, using statistical software, SPSS. Additionally, an independent data analyst was consulted in regards to the confidence interval calculations. Excel was used to calculate the frequency and confidence interval based on the sample size and observed sample proportion. A two-way frequency table analysis assessed the number of consults in which expanded carrier screening yielded positive or negative results with positive or negative FHH findings. The data was also analyzed for the number of consults that received a referral or recommendation for further follow-up based on the reported family history information and the types of follow-up recommendations made. Further analysis was conducted to determine the topics involved during general risk counseling. Discussion topics included known genetic disorders, psychiatric disorders, and various multifactorial conditions, among others.

Results

Consults were screened based on the established inclusion criteria. Eight hundred and sixteen consults were reviewed, of which 316 (38.7%) consults did not meet the inclusion criteria. A total of 500 consults were used in the final analysis. Consults that were excluded from the data set were those that received testing other than the CarrierMap screening panel through Recombine or declined a full family history evaluation. The consults analyzed consisted of 206 (41.2%) couple consults and 294 (58.8%) individual consults (Table 1). The sample population was composed of 482 females and 222 males.

Table 1. **Distribution of Consults**

	Number of Consults	**Proportion of Consults (%)**
Individual	294	58.8
Couple	206	41.2
Total	500	100

Genetic carrier screening indications included: IVF using sperm or egg donor, frozen embryo transfer, infertility evaluation, egg donor screening, egg cryopreservation, and reproductive purposes not otherwise specified (Table 2).

Table 2. ***Indications for Genetic Carrier Screening (n=500)***

Indication	**Number of Consults**	**Proportion of Consults (%)**
Reproductive, not otherwise specified	422	84.4
IVF using sperm donor	21	4.2
IVF using egg donor	8	1.6
IVF using frozen egg	1	0.2
Infertility evaluation	10	2.0
Egg donor screening	23	4.6
Egg cryopreservation	15	3.0

Of the 500 total consults, 310 (62.0%) were consults in which the individual or at least one partner of a couple was identified to be a carrier for at least one genetic condition, and 190 (38.0%) were consults for individuals or couples who did not have a positive result on the CarrierMap screening panel (Table 3).

Table 3. ***Expanded Carrier Screening Results (n=500)***

	Number of Consults	**Proportion of Total Consults (%)**
Positive ECS Result[a]	310	62.0%
Negative ECS Result[b]	190	38.0%

[a]Positive for the individual, or at least one partner (if a couple)
[b]Negative for the individual, or both partners (if a couple)

Within the 310 consults with positive carrier screening, 211 (68.0%) also had family history indications warranting further follow-up, general risk counseling, or both (Table 4). Within the 190 consults that received negative results on expanded carrier screening, 117 (61.6%) had indications warranting further follow-up, general risk counseling, or both (Table 4).

Table 4. ***Genetic Carrier Screening Results with and without Significant FHH Findings (n=500)***		
	Significant Findings in Family History	**No Significant Findings in Family History**
Positive ECS Result[a]	211	99
Negative ECS Result[b]	117	73

[a]Positive for the individual, or at least one partner (if a couple)
[b]Negative for the individual, or both partners (if a couple)

Consults yielded between one and four types of recommendations for follow-up evaluation (Table 5). The 95% confidence interval for the proportion of consults to produce any type of follow-up evaluation is 44.4% ± 4.4%, or 40.0% to 48.8%. One hundred fifty-two consults (30.4%) had only one indication to warrant further follow-up. The 95% confidence interval for consults with only one indication is 30.4% ± 4.0%, or 26.4% to 34.4%. Only two consults in the sample, which make up 0.4% of all consults, had a maximum number of four follow-up indications. The 95% confidence interval for consults that had four indications is 0.4% ± 0.6%, which is not significant by statistical standards for the lower limit.

Table 5. ***Number of Follow-up Recommendations per Consult***			
Number of Recommendations	**Number of Consults**	**Proportion of Total Consults (%)**	**95% Confidence Interval (%)**
0	278	55.6	4.4
1	152	30.4	4.0
2	53	10.6	2.7
3	15	3.0	1.5
4	2	0.4	0.6

Based on family history alone, an overall number of 222 (44.4%) consults had a family history finding that warranted further follow-up, and received either a referral or recommendation for additional evaluation (Table 6).

Table 6. ***Consults with and without Indications for Further Follow-up Based on Family History Alone (n=500)***		
	Number of Consults	**Proportion of Consults (%)**
With indications for further follow-up	222	44.4
Without indications for further follow-up	278	55.6

Recommendations for further evaluation were made to the following subspecialties: cancer genetics, cardiology and cardiovascular genetics, neurogenetics, general genetics evaluation, prenatal ultrasound, infertility work-up, ophthalmology, endocrinology, and specialists based on known familial conditions (Table 7). The family history evaluations elicited cancer genetic counseling recommendations in 141 consults, which comprised of 28.2% of all consults. The 95% confidence interval for follow-up recommendations to cancer genetic counseling is 28.2% ± 3.9%, or 24.3% to 32.1%.

Table 7. ***Recommendations for Further Follow-up Evaluation/Testing Based on Family History***			
Type of Recommendation	**Number of Consults**	**Proportion of Total Consults (%)**	**95% Confidence Interval (%)**
Cancer Genetics	141	28.2	3.9
Genetics Evaluation	55	11.0	2.7
Infertility Work-up	41	8.2	2.4
Neurogenetics	32	6.4	2.1
Cardiovascular Genetics	16	3.2	1.5
Prenatal Ultrasound	16	3.2	1.5
Ophthalmology	3	0.6	0.7
Other	7	1.4	1.0

A total of 233 (46.6%) consults received general risk counseling, which could contain additional risk assessment and/or patient education, for various findings within the family history (Table 8). Topics that prompted general risk counseling included known genetic disorders, psychiatric disorders, autism spectrum disorder, intellectual disability or learning

difficulties, seizures or epilepsy, birth defects, recurrent pregnancy loss or miscarriage, autoimmune disorders, other multifactorial conditions, and infant deaths. Overall, family indications that warranted some form of general risk counseling and patient education were observed in 233 consults, which accounted for approximately 46.6% of all consults (Table 8).

Table 8. ***Consults With and Without Indications for General Risk Counseling Based on Family History Alone (n=500)***

	Number of Consults	**Proportion of Total Consults (%)**
With indications for general risk counseling	233	46.6
Without indications for general risk counseling	267	53.4

The confidence interval for the proportion of consults that had at least one finding to warrant further discussion of reproductive or health risk was 46.6% ± 4.4%, or 42.2% to 51.0% (Table 9). Approximately 33.4% (±4.1%) and 10.2% (± 2.7%) of all consults had one and two indications, respectively, within the family history that warranted additional counseling and education.

Table 9. ***Distribution of the Number of Topics Discussed for General Risk Counseling Per Consult (n=500)***

Number of Topics Discussed	**Number of Consults**	**Proportion of Total Consults (%)**	**95% Confidence Interval (%)**
0	267	53.4	4.4
1	167	33.4	4.1
2	51	10.2	2.7
3	12	2.4	1.3
4	3	0.6	0.7

Of the consults that did receive general risk counseling (n=233), a large proportion belonged to those with only one finding in the family history, which was estimated to be 71.7% with a confidence interval of 5.8%, or 65.9% to 77.5% (Table 10).

Table 10. ***Distribution of the Number of Topics Discussed for General Risk Counseling Per Consult for Consults that Received General Risk Counseling (n=233)***			
Number of Topics Discussed	**Number of Consults**	**Proportion of Consults (%)**	**95% Confidence Interval (%)**
1	167	71.7	5.8
2	51	21.9	5.3
3	12	5.2	2.8
4	3	1.3	1.4

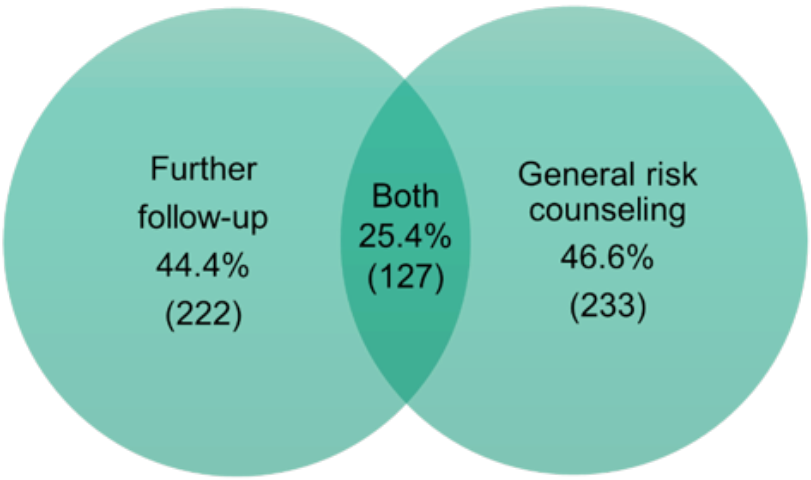
With regards to topics that were elicited during the evaluation, autoimmune disorders and psychiatric conditions emerged as the top two categories at 16.8% and 10.0%, respectively (Table 11). The confidence interval for autoimmune disorders and psychiatric conditions were 3.3% and 2.6%, respectively. Autism spectrum disorders alone accounted for 1.4% of consults with a confidence interval of 1.0%, which also was the lowest incidence category observed.

Table 11. ***Family History Findings that Prompted General Risk Counseling***			
Type of Discussion	**Number of Consults**	**Proportion of Total Consults (%)**	**95% Confidence Interval (%)**
Autoimmune Disorders	84	16.8	3.3
Psychiatric Disorders	50	10.0	2.6
Other/Multifactorial Conditions	39	7.8	2.4
Diagnosed Genetic Conditions	33	6.6	2.2
Birth Defects	32	6.4	2.1
Intellectual Disability/Learning Difficulties	31	6.2	2.1
Epilepsy/Seizures	18	3.6	1.6
RPL/Infertility/Stillbirth	12	2.4	1.3
Neurological Disorders	11	2.2	1.3
Autism Spectrum Disorder	7	1.4	1.0

Overall, 222 consults (44.4% of the total consults) had FHH indications requiring further follow-up and 233 (46.6% of the total consults) had FHH indications requiring

general risk counseling (Figure 1). Of the 500 total, 127 (25.4%) consults had family history indications for both further follow-up and general risk counseling.

Figure 1. Breakdown of Consults with FHH Findings



Discussion

The utility of FHH as a clinical tool was examined by reviewing the type of clinical data obtained from a full family history evaluation. This included analyzing the frequency with which family history evaluations elicited significant findings and characterizing the type of findings observed. Of the 816 consults initially reviewed, 500 consults met inclusion criteria and were used to assess the clinical utility of family history evaluations. Expanded carrier screening yielded positive results in more than half of the consults. For these individuals, the results provided additional insight into their reproductive risk and elucidated further testing options for the partner, gamete donor, or intended parent(s). Follow-up testing options included expanded carrier screening, targeted gene sequencing, or non-genetic laboratory testing, such as a complete blood count and quantitative hemoglobin electrophoresis.

The type of information elicited from the family history evaluation can be characterized into two categories: information that prompted recommendation for further follow-up and information that prompted general risk counseling, which could include risk assessment and patient education. Overall, a quarter of the total consults had findings within the family history that warranted both further follow-up and general risk counseling, regardless of carrier screening results. Information elicited during these particular consults prompted follow-up recommendations and also yielded additional insight into the individual's and/or couple's reproductive or personal health risk. Of the 310 consults with positive carrier screening results, over two-thirds (68.0%) had additional indications in their family history that warranted further evaluation, general risk counseling, or both. For these individuals and couples, FHH prompted additional considerations to reproductive and personal health risks that otherwise were not detected through expanded carrier screening. Of the 190 consults with negative carrier screening results, over three-fifths (61.6%) had family history indications that warranted further evaluation, general risk counseling, or both.

Without a family history evaluation, close to one-fifth (23.4%) of the 500 total consults with familial findings that affected the individual or couple's reproductive or personal health risk would have been missed. This frequency is comparable to that of previously conducted studies which looked at the frequency of family history findings in patients without previously identified genetic concerns. A study by Hafen et al. reviewed family history data for 700 women and found that a total of 28.4% had some sort of family history finding (Hafen et al., 2009). Of the 28.4% of women with family history findings, about 19.1% had a family history "positive" for birth defect or genetic condition with a minimal/low risk of recurrence, in which additional evaluation/genetic testing during

pregnancy was not indicated, while about 9.3% had family histories “significant” for birth defect or genetic condition with an increased risk of recurrence, in which additional evaluation/genetic testing during the pregnancy was indicated. Additional studies looking at women who were referred for amniocentesis found the frequency of significant family history findings to be around 10 to 43% (Cohn et al., 1999; Holzgreve et al., 1983; Langer and Kudart, 1990; Meschede et al., 2000; Rubin et al., 1983). The frequency of 23.4% ascertained in this study falls within with the range observed in these previously conducted studies and is lower than that of Hafen’s study. The differences in the frequencies can be accounted for by the parameters used to determine and categorize the significance of family history data as well as the demographics of the population sampled. These factors limit the extent to which the findings can be generalizable to other prenatal patient populations since this study’s cohort was ascertained specifically from a population for which carrier screening was indicated.

FHH, when considered alone, yielded clinically actionable data which prompted follow-up recommendations in 222 consults (44.4% of the total consults). This included recommendations for follow-up with cancer genetic counseling, cardiology and cardiovascular genetics, neurogenetics, a general genetics evaluation, a prenatal ultrasound, an infertility work-up, and other subspecialties including ophthalmology, audiology, dermatology, and endocrinology. The results of the study indicated that family history evaluations were most likely to identify to cancer indications, which produced follow-up recommendations for cancer genetic counseling in over a quarter of the total number of consults. The second highest number of recommendations made was to a general genetics provider; this composed over 10% of total consults. An overwhelming majority of these

genetic evaluation recommendations were due to a diagnosis of an autism spectrum disorder (ASD) within the family. It was observed that the option of an ASD evaluation to identify the underlying cause was dependent on the discretion of the genetic counselor conducting the session, as some counselors were more likely to refer, irrespective of the degree of relation to the individual or couple.

Oftentimes, a family history evaluation led to multiple follow-up recommendations; it was observed that each consult yielded follow-up recommendations for between one to four different types of evaluations. Almost one-third of all consults had one recommendation for an additional evaluation. Four recommendations were warranted in two of the 500 consults (less than half of one percent). With only two observed in a sample size of 500, consults with four different recommendations yielded an insignificant lower confidence bound.

Some consults had family-history-based findings that elicited discussions on general risk counseling. For these particular consults, genetic counselors provided risk assessment and patient education as needed. Topics that came up per patient report included known genetic disorders within the family, psychiatric disorders, autism spectrum disorders, intellectual disability or learning difficulties, seizures or epilepsy, birth defects, recurrent pregnancy loss or stillbirth, autoimmune disorders, and other findings including additional multifactorial conditions and infant deaths. In close to half of the total consults, general risk counseling was provided, which added additional perspective to the reproductive or personal health risk information for the individual or couple. General risk counseling occurred most frequently for autoimmune disorders, which was discussed in 16.8% of the consults. Some of the major disorders most frequently discussed were diabetes, lupus, thyroid disorders, and multiple sclerosis. These results have implications for genetic counseling practices,

particularly with regards to patient education. Such FHH findings provide opportunities for patient education by prompting discussion of co-genetic susceptibility. Psychiatric disorders prompted general risk counseling in approximately 10% of all consults, emerging as the second most frequently discussed topic. The most frequently discussed psychiatric disorders included depression, bipolar disorder, and schizophrenia. A positive family history is the greatest recognized risk factor for developing conditions such as schizophrenia and major depression (Laursen et al., 2005; Austin and Peay, 2006). Although predictive genetic testing is currently not available for these conditions, the relevance of genetic counseling is not limited by the absence of testing (Jenkins & Arribas-Ayllon, 2016). Past studies have found that providing patient education about etiology offer many benefits to affected individuals and their families (Austin & Honer, 2008; Hippman et al., 2013, 2016). Patient education serves to improve knowledge, alleviate anxiety, and increase risk perception accuracy in those with heightened concern about their risk to develop a mental illness (2008; 2013; 2016). The frequency with which psychiatric conditions came up in this study highlights the value of genetic counseling for individuals with positive family histories, who may benefit from patient education and counseling. For this study, general risk counseling for ASD was also provided in a little over 1% of all consults; a recurrence risk score was given as part of general risk counseling and was calculated based on the degree of relation of the family member affected with ASD. For these particular consults with positive family histories for ASD, it was determined that a recommendation for a genetics evaluation was not necessary but a discussion of reproductive risk was still warranted. Whether a family finding of ASD prompted a recommendation for further follow-up or general risk counseling was made at the genetic counselor's discretion. For all of these cases discussed, additional information and

insight were gained through general risk counseling and patient education; however, this information did not prompt further actions or evaluations for the individual or couple.

The results of this study are subject to inherent limitations of the data. The inclusion criteria for the study restricted the population sample to individuals and couples that received expanded carrier screening through Recombine, thereby limiting the overall diversity of the patient population. Therefore, these results may only be applicable to genetic counseling consults that occur in context of an expanded carrier screening setting. Reported information was also subject to the genetic counselor's assessment of its importance and relevance to the consult. The information available through each consult's chart notes and consult letter may not reflect all the details of the consult. This limitation is compounded by the influence of counselor differences such as style, technique, and experience, all of which contribute to the specific information collected or recorded during a consult. For example, in some cases, recommendations were included in the consult letter irrespective of the finding's actual level of significance, relative reproductive risk to the individual or couple, or level of patient concern. Counselor discretion also played a role in whether a family history finding yielded a recommendation for follow-up or general risk counseling. Specific cases of this were observed in cases that involved recurrent pregnancy loss and autism spectrum disorder findings.

Only a small body of research exists on the clinical utility of FHH evaluations. Overall, the results of this study provide insights into the type of information that can be elicited through a FHH evaluation. FHH provides supplemental information to the individual or couple's expanded carrier screening results, which adds to knowledge of personal health risk and reproductive risk. The frequency with which relevant findings were elicited during a

family history evaluation also offers further support to its utility as a clinical tool in the patient-care setting. Family history studies can serve as a useful evaluation tool for non-routine screening procedures, diagnostic testing, and referral to genetic counseling in different disciplines (Beadles et al., 2014). Furthermore, FHH can be used as a screening tool to identify individuals who would benefit from further evaluation, additional risk counseling, or patient education. The results of this study provide support to the broader adoption of FHH evaluations in routine clinical care, which further warrants the use of genetic counselors in healthcare environments outside of traditional genetic settings (Wilson et al., 2012). The implementation of thorough FHH as a routine clinical tool would enable better care and risk management for patients and their families (Brock et al., 2010; Tarini & McInerney, 2013; Wu et al., 2015). FHH, however, remains an underutilized tool for risk assessment in primary care settings (Langlands, Prentice, & Ravine, 2010; Powell et al., 2013; Tarini & McInerney, 2013). A number of studies have found that FHH data collected in primary care settings lacks the completeness needed to be used effectively as a risk assessment tool (Powell et al., 2013; Tarini & McInerney, 2013; B. J. Wilson et al., 2012). This further emphasizes the need for genetic counseling and genetics consultations to be performed by certified genetic professionals. Correct interpretation of FHH requires in-depth genetics knowledge that ensures accurate risk assessments, proper risk counseling, and appropriate recommendations for follow-up.

The study also provides perspective on patient's understanding and knowledge of their own FHH as well as insight into health topics that were of highest patient concern. Further studies should look into how patients can prepare for a genetics consultation in order to obtain the most optimal outcome. A patient's knowledge of relevant FHH information

better enables healthcare professionals to personalize the care plan and management to a patient's risks and needs. From a provider's perspective, the results of this study elucidated on health topics and conditions that tend to come up more frequently than others during a FHH evaluation. This may then provide insight into the type of topics that can be expected to come up during a genetics consultation. Awareness and knowledge of these topics may be beneficial to genetic professionals as this can help facilitate risk assessment and counseling. As medicine moves away from the "one size fits all model", the critical role of FHH in personalized medicine has become more apparent than ever. FHH is an easy and simple tool with high clinical utility that warrants its adoption into a variety of routine healthcare settings.

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Appendix A: *List of Diseases Included on CarrierMap Testing*

Disease Name
11-Beta-Hydroxylase-Deficient Congenital Adrenal Hyperplasia
17-Alpha-Hydroxylase Deficiency
17-Beta-Hydroxysteroid Dehydrogenase Deficiency
21-Hydroxylase-Deficient Classical Congenital Adrenal Hyperplasia
21-Hydroxylase-Deficient Nonclassical Congenital Adrenal Hyperplasia
3-Beta-Hydroxysteroid Dehydrogenase Deficiency
3-Methylcrotonyl-CoA Carboxylase Deficiency: MCCA Related
3-Methylcrotonyl-CoA Carboxylase Deficiency: MCCB Related
3-Methylglutaconic Aciduria: Type 3
3-Phosphoglycerate Dehydrogenase Deficiency
5-Alpha Reductase Deficiency
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency
ARSACS
Abetalipoproteinemia
Acrodermatitis Enteropathica
Acute Infantile Liver Failure: TRMU Related
Acyl-CoA Oxidase I Deficiency
Adenosine Deaminase Deficiency
Adrenoleukodystrophy: X-Linked
Alkaptonuria
Alpha Thalassemia
Alpha-1-Antitrypsin Deficiency
Alpha-Mannosidosis
Alport Syndrome: COL4A3 Related
Alport Syndrome: COL4A4 Related
Alport Syndrome: X-linked
Amegakaryocytic Thrombocytopenia
Andermann Syndrome
Androgen Insensitivity Syndrome: Complete
Antley-Bixler Syndrome
Argininemia
Argininosuccinate Lyase Deficiency
Aromatase Deficiency
Arthrogryposis, Mental Retardation, & Seizures
Arts Syndrome
Asparagine Synthetase Deficiency
Aspartylglycosaminuria
Ataxia with Vitamin E Deficiency

Disease Name
Ataxia-Telangiectasia
Autosomal Recessive Polycystic Kidney Disease
Bardet-Biedl Syndrome: BBS1 Related
Bardet-Biedl Syndrome: BBS10 Related
Bardet-Biedl Syndrome: BBS11 Related
Bardet-Biedl Syndrome: BBS12 Related
Bardet-Biedl Syndrome: BBS2 Related
Bare Lymphocyte Syndrome: Type II
Bartter Syndrome: Type 4A
Beta Thalassemia
Beta-Hexosaminidase Pseudodeficiency
Beta-Ketothiolase Deficiency
Biotinidase Deficiency
Bloom Syndrome
Canavan Disease
Carnitine Palmitoyltransferase IA Deficiency
Carnitine Palmitoyltransferase II Deficiency
Carnitine-Acylcarnitine Translocase Deficiency
Carpenter Syndrome
Cartilage-Hair Hypoplasia
Cerebrotendinous Xanthomatosis
Charcot-Marie-Tooth Disease with Deafness: X-Linked: GJB1 Related
Charcot-Marie-Tooth Disease with Deafness: X-Linked: PRPS1 Related
Chediak-Higashi Syndrome
Cholesteryl Ester Storage Disease
Choreoacanthocytosis
Choroideremia
Chronic Granulomatous Disease: CYBA Related
Chronic Granulomatous Disease: X-Linked
Citrin Deficiency
Citrullinemia: Type I
Classical Galactosemia
Cockayne Syndrome: Type A
Cockayne Syndrome: Type B
Cohen Syndrome
Combined Pituitary Hormone Deficiency: PROP1 Related
Congenital Disorder of Glycosylation: Type 1A: PMM2 Related
Congenital Disorder of Glycosylation: Type 1B: MPI Related
Congenital Disorder of Glycosylation: Type 1C: ALG6 Related

Disease Name
Congenital Ichthyosis: ABCA12 Related
Congenital Insensitivity to Pain with Anhidrosis
Congenital Lipoid Adrenal Hyperplasia
Congenital Myasthenic Syndrome: CHRNE Related
Congenital Myasthenic Syndrome: DOK7 Related
Congenital Myasthenic Syndrome: RAPSN Related
Congenital Neutropenia: Recessive
Copper Transport Disorders
Corneal Dystrophy and Perceptive Deafness
Corticosterone Methyloxidase Deficiency
Crigler-Najjar Syndrome
Cystic Fibrosis
Cystinosis
Cystinuria: Non-Type I
Cystinuria: Type I
D-Bifunctional Protein Deficiency
DMD-Related Muscular Dystrophies
Diabetes: Recessive Permanent Neonatal
Du Pan Syndrome
Dyskeratosis Congenita: RTEL1 Related
Dystrophic Epidermolysis Bullosa: Recessive
Ehlers-Danlos Syndrome: Type VIIC
Ellis-van Creveld Syndrome: EVC Related
Ellis-van Creveld Syndrome: EVC2 Related
Emery-Dreifuss Myopathy: X-Linked
Enhanced S-Cone
Ethylmalonic Aciduria
Fabry's Disease
Factor IX Deficiency
Factor VIII Deficiency
Familial Chloride Diarrhea
Familial Dysautonomia
Familial Hyperinsulinism: Type 1: ABCC8 Related
Familial Hyperinsulinism: Type 2: KCNJ11 Related
Familial Mediterranean Fever
Fanconi Anemia: Type A
Fanconi Anemia: Type C
Fanconi Anemia: Type G
Fanconi Anemia: Type J

Disease Name
Fragile X Syndrome
Fumarase Deficiency
GM1-Gangliosidoses
GRACILE Syndrome
Galactokinase Deficiency
Gaucher Disease
Gitelman Syndrome
Globoid Cell Leukodystrophy
Glucose-6-Phosphate Dehydrogenase Deficiency
Glutaric Acidemia: Type I
Glutaric Acidemia: Type IIA
Glutaric Acidemia: Type IIB
Glutaric Acidemia: Type IIC
Glycine Encephalopathy: AMT Related
Glycine Encephalopathy: GLDC Related
Glycogen Storage Disease: Type IA
Glycogen Storage Disease: Type IB
Glycogen Storage Disease: Type II
Glycogen Storage Disease: Type III
Glycogen Storage Disease: Type IV
Glycogen Storage Disease: Type V
Glycogen Storage Disease: Type VII
Guanidinoacetate Methyltransferase Deficiency
HMG-CoA Lyase Deficiency
Hemochromatosis: Type 2A: HFE2 Related
Hemochromatosis: Type 3: TFR2 Related
Hemoglobinopathy: Hb C
Hemoglobinopathy: Hb D
Hemoglobinopathy: Hb E
Hemoglobinopathy: Hb O
Hereditary Fructose Intolerance
Hereditary Spastic Paraplegia: TECPR2 Related
Herlitz Junctional Epidermolysis Bullosa: LAMA3 Related
Herlitz Junctional Epidermolysis Bullosa: LAMB3 Related
Herlitz Junctional Epidermolysis Bullosa: LAMC2 Related
Hermansky-Pudlak Syndrome: Type 1
Hermansky-Pudlak Syndrome: Type 3
Hermansky-Pudlak Syndrome: Type 4
Holocarboxylase Synthetase Deficiency

Disease Name
Homocystinuria Caused by CBS Deficiency
Hunter Syndrome
Hurler Syndrome
Hypohidrotic Ectodermal Dysplasia: X-Linked
Hypophosphatasia
Inclusion Body Myopathy: Type 2
Infantile Cerebral and Cerebellar Atrophy
Isolated Microphthalmia: VSX2 Related
Isovaleric Acidemia
Joubert Syndrome
Juvenile Retinoschisis: X-Linked
Lamellar Ichthyosis: Type 1
Laryngoonychocutaneous Syndrome
Leber Congenital Amaurosis: CEP290 Related
Leber Congenital Amaurosis: GUCY2D Related
Leber Congenital Amaurosis: LCA5 Related
Leber Congenital Amaurosis: RDH12 Related
Leigh Syndrome: French-Canadian
Leukoencephalopathy with Vanishing White Matter: EIF2B5 Related
Leydig Cell Hypoplasia (Luteinizing Hormone Resistance)
Limb-Girdle Muscular Dystrophy: Type 2A
Limb-Girdle Muscular Dystrophy: Type 2B
Limb-Girdle Muscular Dystrophy: Type 2C
Limb-Girdle Muscular Dystrophy: Type 2D
Limb-Girdle Muscular Dystrophy: Type 2E
Limb-Girdle Muscular Dystrophy: Type 2F
Limb-Girdle Muscular Dystrophy: Type 2I
Lipoprotein Lipase Deficiency
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency
Lowe Oculocerebrorenal Syndrome
Lysinuric Protein Intolerance
MTHFR Deficiency: Severe
Malonyl-CoA Decarboxylase Deficiency
Maple Syrup Urine Disease: Type 1A
Maple Syrup Urine Disease: Type 1B
Maple Syrup Urine Disease: Type 2
Maple Syrup Urine Disease: Type 3
Maroteaux-Lamy Syndrome
Meckel Syndrome: Type 1

Disease Name
Medium-Chain Acyl-CoA Dehydrogenase Deficiency
Megalencephalic Leukoencephalopathy
Metachromatic Leukodystrophy
Methylmalonic Acidemia: MMAA Related
Methylmalonic Acidemia: MMAB Related
Methylmalonic Acidemia: MUT Related
Methylmalonic Aciduria and Homocystinuria: Type cblC
Mitochondrial Complex I Deficiency: NDUFS6 Related
Mitochondrial DNA Depletion Syndrome: MNGIE Type
Mitochondrial Myopathy and Sideroblastic Anemia
Mitochondrial Trifunctional Protein Deficiency: HADHB Related
Morquio Syndrome: Type A
Morquio Syndrome: Type B
Mucolipidosis: Type II/III
Mucolipidosis: Type IV
Multiple Pterygium Syndrome
Multiple Sulfatase Deficiency
Muscle-Eye-Brain Disease
Myotubular Myopathy: X-Linked
Navajo Neurohepatopathy
Nemaline Myopathy: NEB Related
Nephrotic Syndrome: Type 1
Nephrotic Syndrome: Type 2
Neuronal Ceroid-Lipofuscinosis: CLN5 Related
Neuronal Ceroid-Lipofuscinosis: CLN6 Related
Neuronal Ceroid-Lipofuscinosis: CLN8 Related
Neuronal Ceroid-Lipofuscinosis: MFSD8 Related
Neuronal Ceroid-Lipofuscinosis: PPT1 Related
Neuronal Ceroid-Lipofuscinosis: TPP1 Related
Niemann-Pick Disease: Type A
Niemann-Pick Disease: Type B
Niemann-Pick Disease: Type C1
Niemann-Pick Disease: Type C2
Nijmegen Breakage Syndrome
Nonsyndromic Hearing Loss and Deafness: GJB2 Related
Nonsyndromic Hearing Loss and Deafness: LOXHD1 Related
Nonsyndromic Hearing Loss and Deafness: MYO15A Related
Oculocutaneous Albinism: Type 1
Oculocutaneous Albinism: Type 3

Disease Name
Oculocutaneous Albinism: Type 4
Omenn Syndrome: DCLRE1C Related
Omenn Syndrome: RAG2 Related
Ornithine Transcarbamylase Deficiency
Ornithine Translocase Deficiency
Osteopetrosis: TCIRG1 Related
POLG Related Disorders: Autosomal Recessive
Papillon-Lefevre Syndrome
Pendred Syndrome
Persistent Mullerian Duct Syndrome: Type I
Persistent Mullerian Duct Syndrome: Type II
Phenylalanine Hydroxylase Deficiency
Polyglandular Autoimmune Syndrome: Type I
Pontocerebellar Hypoplasia: EXOSC3 Related
Pontocerebellar Hypoplasia: RARS2 Related
Pontocerebellar Hypoplasia: SEPSECS Related
Pontocerebellar Hypoplasia: TSEN54 Related
Pontocerebellar Hypoplasia: VPS53 Related
Pontocerebellar Hypoplasia: VRK1 Related
Primary Carnitine Deficiency
Primary Ciliary Dyskinesia: DNAI1 Related
Primary Ciliary Dyskinesia: DNAI2 Related
Primary Congenital Glaucoma
Primary Hyperoxaluria: Type 1
Primary Hyperoxaluria: Type 2
Primary Hyperoxaluria: Type 3
Progressive Familial Intrahepatic Cholestasis: Type 2
Propionic Acidemia: PCCA Related
Propionic Acidemia: PCCB Related
Pseudocholinesterase Deficiency
Pycnodysostosis
Pyruvate Carboxylase Deficiency
Pyruvate Dehydrogenase Deficiency
Pyruvate Dehydrogenase Deficiency: X-Linked
Renal Tubular Acidosis and Deafness
Retinal Dystrophies: RLBP1 Related
Retinal Dystrophies: RPE65 Related
Retinitis Pigmentosa: CERKL Related
Retinitis Pigmentosa: DHDDS Related

Disease Name
Retinitis Pigmentosa: FAM161A Related
Rhizomelic Chondrodysplasia Punctata: Type I
SCID: X-Linked
Salla Disease
Sandhoff Disease
Sanfilippo Syndrome: Type A
Sanfilippo Syndrome: Type B
Sanfilippo Syndrome: Type C
Sanfilippo Syndrome: Type D
Short-Chain Acyl-CoA Dehydrogenase Deficiency
Sickle-Cell Anemia
Sjogren-Larsson Syndrome
Sly Syndrome
Smith-Lemli-Opitz Syndrome
Spinal Muscular Atrophy: SMN1 Linked
Stargardt Disease
Stuve-Wiedemann Syndrome
Sulfate Transporter-Related Osteochondrodysplasia
Tay-Sachs Disease
Trichohepatoenteric Syndrome: Type 1
Tyrosine Hydroxylase Deficiency
Tyrosinemia: Type I
Tyrosinemia: Type II
Usher Syndrome: Type 1B
Usher Syndrome: Type 1C
Usher Syndrome: Type 1D
Usher Syndrome: Type 1F
Usher Syndrome: Type 2A
Usher Syndrome: Type 3
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency
Walker-Warburg Syndrome
Werner Syndrome
Wilson Disease
Wiskott-Aldrich Syndrome
Wolcott-Rallison Syndrome
Wolman Disease
Xeroderma Pigmentosum: Group A
Xeroderma Pigmentosum: Group C
Zellweger Spectrum Disorders: PEX1 Related

Disease Name
Zellweger Spectrum Disorders: PEX10 Related
Zellweger Spectrum Disorders: PEX2 Related
Zellweger Spectrum Disorders: PEX6 Related