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Qualitative Research

Does genetic testing offer utility as a supplement to traditional family health history intake for inherited disease risk?

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Content: This study examines the potential utility of genetic testing as a supplement to family health history to screen for increased risk of inherited disease. Medical conditions are often misreported or misunderstood, especially those related to different forms of cardiac disease (arrhythmias vs. structural heart disease vs. coronary artery disease), female organ cancers (uterine vs. ovarian vs. cervical), and type of cancer (differentiating primary cancer from metastases to other organs). While these nuances appear subtle, they can dramatically alter medical management. For example, different types of cardiac failure (structural, arrhythmia, and coronary artery disease) have inherited forms that are managed with vastly different approaches.

Methods: Using a dataset of over 6,200 individuals who underwent genetic screening, we compared the ability of genetic testing and traditional family health history to identify increased risk of inherited disease. A further, in-depth qualitative study of individuals for whom risk identified through each method was discordant, explored whether this discordance could be addressed through changes in family health history intake.

Findings: Of 90 individuals for whom genetic testing indicated significant increased risk for inherited disease, two-thirds (66%) had no corroborating family health history. Specifically, we identify cardiomyopathy, arrhythmia, and malignant hyperthermia as conditions for which discordance between genetic testing and traditional family health history was greatest, and familial hypercholesterolaemia, Lynch syndrome, and hereditary breast and ovarian cancer as conditions for which greater concordance existed.

Conclusion: We conclude that genetic testing offers utility as a supplement to traditional family health history intake over certain conditions.

Key words: family health history, genetic screening, inherited disease risk, preventive health

Introduction and background

Family health history (FHx) represents the first iteration of genetic screening, and remains the most commonly utilized screening tool for inherited disease risk. Although FHx has proven to be extremely effective as a screening tool over many conditions, it remains a flawed tool in its reliance on complete and accurate family communication.[1] This can be quite challenging. The information needed to successfully interpret FHx includes complex information on 3 generations of relatives, such as how the relative is related, the gender of the relative, the relative's medical conditions and how old he/she was when the condition started, and, if alive, their current age or, if deceased, the age and cause of death. Medical conditions in particular are often misreported or misunderstood, especially those related to different forms of cardiac disease (arrhythmias vs. structural heart disease vs. coronary artery disease), female organ cancers (uterine vs. ovarian vs. cervical), and type of cancer (differentiating primary cancer from metastases to other organs).

While the above nuances appear subtle, they can dramatically alter the interpretation of the family history. For example, a family history of uterine or ovarian cancer raises suspicion for an inherited disease such as Lynch syndrome, whereas cervical cancer does not. In cardiac disease, most individuals describe cardiac failure as a "heart attack," but all 3 types of cardiac failure (structural, arrhythmia, and coronary artery disease) have inherited forms that are managed with vastly different approaches. Clinicians and researchers that rely on having an accurate FHx have employed techniques to overcome these barriers, though there is a tradeoff between increased accuracy and patient and provider burden. Simpler options include providing worksheets with details about what information to gather and how to approach relatives, while more complex options include accessing relatives' medical records (which requires the relative's permission and access to their provider). More recently, technology has the potential to streamline the process through linking and sharing of electronic medical records.

With the advent of genomic approaches, including genotyping for single nucleotide variants and exome or

Key messages

- Genetic testing is a useful supplement to traditional family health history.
- Genetic testing and family history have different strengths assessing risk.
- Genetic testing adds valuable nuance to risk identified by family history.

genome sequencing, the potential for genetic testing to provide a more objective basis for assessing inherited disease risk has been contemplated.[2] This promise, however, has faced obstacles due to limitations in traditional application of genetic testing for screening purposes. Interpretation of genetic test results has traditionally been done in the context of testing of multiple family members (e.g. "triad testing" of mother, father, and offspring). In addition, issues of cost-effectiveness inevitably arise for any population-level intervention. Although testing for limited genetic panels is commonly available for between $100–$200 dollars (and so is not, in a health care context, exorbitant on a *per test* basis), even a small cost for testing can become significant when multiplied by millions of iterations within a given population. This will require provision of significant evidence of value in order for this intervention to become adopted.

Early studies comparing the ability of "genetic testing" vs. traditional FHx to identify risk of inherited disease indicated that testing added little value to traditional FHx assessment at a population level, undermining the justification for testing's higher cost.[3,4] Because traditional FHx requires no testing, this remains the default for most populations. Although genetic testing may be cost-effective for defined populations that lack access to traditional family history,[5–7] for *general screening purposes* the most promising strategies both in terms of documented utility and cost-effectiveness of genetic testing have been tied to forms of "cascade testing" that rely on familial relationships with persons who have been diagnosed with a disease to indicate testing is warranted, rather than screening of the general population.[8,9]

The utility and cost-effectiveness of genetic testing for the general population remain undocumented.[10] This has led a 2021 AHRQ report developed to guide United States Preventive Services Task Force (USPSTF) policy to conclude:

> The evidence base for health outcomes and harms associated with genomic screening and risk prediction is beginning to develop, and information on health outcomes should be available within the next 5 years. Potential implications of genomic screening for USPSTF methods include unique considerations of test accuracy, inclusion of nontraditional harms and secondary findings, and consideration of expanded positive outcomes, such as personal utility and benefits to family members.[11]

Towards this evidence base we offer below findings from a joint University of Alabama Birmingham—HudsonAlpha Institute for Biotechnology population screening research program: the Alabama Genomic Health Initiative (AGHI). AGHI is a state-funded initiative that provides both rare disease diagnostic testing and population-level testing of genes derived from the American College of Medical Genetics and Genomics (ACMG) recommendations for actionable gene–disease associations suitable for universal investigation as secondary findings whenever genetic testing is performed. AGHI was launched in 2017, and at the time of our data collection had enrolled 6,225 individuals in the population cohort, with approximately 75% of participants female. Racial demographics included 73% White, 20% Black or African-American, 2% Asian, and 5% other/unknown at the time our data were collected. A full description of this initiative, as well as broad findings for both rare diagnostic and population cohorts, was published in 2021.[12]

Below, we first describe AGHI's ability to identify inherited disease risk for ostensibly healthy (nonsymptomatic) individuals over a defined set of conditions, using both traditional FHx intake, and then through genetic screening. Discordance arises when either a family history suggests an inherited condition but genetic testing does not or when genetic testing identified an inherited condition but family history does not. In the first scenario, individuals are still considered at high risk for the condition as there may be a pathogenic variant that the scientific community is not yet aware of or the risk may be driven by environmental exposures. In the second scenario, a family history can add greater nuance to the level of risk imposed by the genetic variant. For example, a strong family history increases the likelihood of developing breast cancer in those with a pathogenic *PALB2* variant by 1½ fold.[13] However, variable expressivity and incomplete penetrance, hallmarks of many genetic disorders, make family history screening alone potentially insufficient at characterizing a person's genetic risk—even when complete and reliable family history information is available. Conversely, in the case of multifactorial disorders, the lack of known single-gene associations with these conditions renders genetic screening largely unhelpful, and family history is heavily relied upon to determine a patient's risk, with 1 example of this approach used for type 2 diabetes.[14]

In all, 3,195—just over half (51.3%)—of AGHI population cohort participants reported family health history that was "flagged" as suggestive of elevated inherited disease risk. Separately, genetic testing identified 91 positive results among 90 individuals (~1.5%) in the population cohort. Discordance between these results existed in several areas. Unsurprisingly, over many conditions, traditional FHx intake proved more effective in identifying increased risk. For some conditions, however, genetic screening proved more effective in identifying increased risk.

Discordance in the direction of elevated risk identified by FHx that is not indicated by genetic screening is unsurprising, for a couple of reasons. First, genetic screening for AGHI was limited to a list of medically actionable genome variants based on the ACMG SF list.[15] Inherited disease explored through FHx intake is known to be much broader than this limited set of gene–disease associations. Second, it may well be the case that a particular individual does not inherit the disease-causing variant that "runs in the family" as results in increased incidence of the disease for that family. Finally, the

field of genetic screening remains at a relatively nascent stage, as evidenced by the rapid expansion of the ACMG genes recommended for investigation as secondary findings, from the original 56 less than a decade ago,[16] to the 73 recommended for investigation today.[17] It is already clear, then, that traditional FHx intake will continue to serve a vital role in health screening for the foreseeable future.

For this reason, we devoted our attention to the discordance between elevated risk identified by positive genetic test results, and the lack of similar risk as identified through FHx intake. This discordance is potentially informative for genetic testing's potential utility as a supplement to FHx. Such utility, however, is relative to the inability to resolve this discordance through less expensive means, especially improvements in FHx intake.

We therefore conducted structured interviews with individuals for whom risk identification was discordant between genetic testing and traditional FHx intake, to explore if this discordance might be explained by inadequate intake procedures, poor understanding of intake questions, or gaps in knowledge about FHx. On the basis of this study, we conclude that genetic screening holds promise as a supplement to FHx, particularly over certain conditions, although it should not be seen as a replacement for such screening.

AGHI: risk identification through FHx and genetic screening

The population cohort of AGHI is designed to provide inherited disease risk assessment to individuals throughout the state of Alabama through both genetic testing and through assessment of family history provided by participants upon intake to AGHI. Recruitment seeks to reflect the diversity of the state, and occurred both at clinics located in various regions, as well as "pop-up" clinics designed to reach individuals in rural and outlying areas, as well as individuals for whom clinical care is less accessible for a variety of reasons.[18]

Methods

Prior to testing, participants complete an FHx intake via a paper questionnaire (see Supplementary Materials) that specifically elicits information about conditions associated with genes investigated through genotyping used for the AGHI population cohort. Genetic counselling staff members then review and triage this information using a set of criteria based on clinical experience and current guidelines for identifying patients and families at increased risk for select inherited conditions.[13,19–21] This high-risk history was further divided into "red" (high risk) or "yellow" (moderate risk) categories for some reported phenotypes to account for more modest increases in risk in select cases. High-risk FHx was communicated with all participants via their result letter and with those with positive genotyping results via the result disclosure phone call.

Results

Of the self-reported personal and family histories of the 90 participants in the AGHI that ultimately received a positive disease risk result, 73% (n = 66) were suggestive of an elevated disease risk. However, of the 66 individuals with a positive genotyping result and a family or personal history flagged as high risk, 44 (67%) had concerning family or personal histories that were not related to their genotyping result. This includes 11 individuals that reported high-risk histories both related and unrelated to their result. Fourteen individuals had a personal history indicative of a genetic risk factor. Twenty-six individuals had a high-risk personal or family history related to 1 or more cardiovascular phenotypes, 23 had such a history related to cancer, and 1 individual had a high-risk family history related to another result category (ornithine transcarbamylase deficiency). Six of these individuals had high-risk personal and/or family history items related to both cancer and cardiovascular conditions (Table 1).

When only considering those histories relevant to the condition(s) associated with their genotyping result, the proportion of individuals flagged dropped to 36% (n = 33). This indicates that nearly 2/3 of the individuals receiving genotyping results indicative of an increased disease risk were receiving risk information that may not have been available to them using family and personal disease history alone. In the absence of the genetic screening results, these individuals would likely be assessed at or near population risk for the associated condition(s).

A couple of example cases are illustrative in this regard. One participant with a particularly complex FHx reported a personal history of hypercholesterolaemia and multiple family members with the same, including one first degree relative diagnosed at age 20. This participant also reported a strong family history of breast cancer, including one second degree relative diagnosed at age 45. These items met our criteria for a "high-risk" FHx of both hypercholesterolaemia and breast cancer—but the participant's genotyping result was a pathogenic variant in *MYBPC3*, associated

Table 1. High-risk personal and family history items reported among 90 participants with positive results, unrelated to result.

Phenotype	# of individuals reporting a personal and/or family history
Cardiovascular conditions	26[a]
Heart attack/cardiac arrest before age 50	12[b]
Arrhythmia	6[b]
High cholesterol	6[b]
Cardiomyopathy	3[b]
Cancer	23[a]
Breast	11[b]
Ovarian	11[b]
Kidney	3
Uterine	1
Melanoma	1[b]
Prostate	1
Bone	1
Brain	1
Other: ornithine transcarbamylase deficiency	1

[a]Number of individuals reporting individual phenotypes in each category is greater than these values due to individuals with multiple reported phenotypes in each category.
[b]Includes 1 or more individuals reporting a *personal* history of this condition.

with hypertrophic cardiomyopathy. This participant reported no personal or family history related to this condition. Another participant with a reported personal history of cardiomyopathy diagnosed at age 19 received a genotyping result indicating a pathogenic variant in *BRCA2*, associated with hereditary breast and ovarian cancer. This participant reported no personal or family history of cancer with the exception of a single relative with colon cancer. Thus, the genetic test results for each of these already high-risk participants were able to add information that can be used to manage them and their chances to develop conditions that, based on reported FHx alone, might otherwise have been overlooked.

Notably, corroboration between family history and genotyping result varied by associated phenotype (Table 2). Hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolaemia were among those conditions with higher concordance, while cardiomyopathy, arrhythmia, and malignant hyperthermia demonstrated lower concordance. Recent understanding of penetrance in inherited heart diseases may provide an explanation for the family history discordance among cardiovascular results.[22] Additionally, some have argued for evaluating polygenic variation when considering risk for inherited cardiac conditions, even in the presence of variants traditionally considered causative of monogenic disease.[23] As malignant hyperthermia commonly presents only after exposure to particular agents,[24] the low rate of concordance for this condition is not surprising.

Strengths of our approach include the provision of an FHx risk assessment prior to and independent of the genotyping process. These data provide a potential argument in favour of the use of genomic screening even for those individuals for whom complete and reliable family history is available. Limitations to consider when reviewing these data include the reliance upon self-reported personal and family medical histories elicited. An additional limitation to our approach in calculating this concordance is the use of a structured family health history questionnaire, an unvalidated tool that may not accurately elicit all relevant information. In addition, incomplete penetrance of inherited disease, lack of access to medical care and screenings, and varying styles of communication about medical information within a family may all contribute to the discordance between genotyping results and personal/family history seen here. See our full description of AGHI for more detailed analysis of the study.[12]

For the above reasons, as well as the potential for other alternative explanations for discordance between risk identified through traditional family health history and risk identified through genetic testing, we felt it important to study whether discordance might be addressed through improvements to FHx intake.

Investigating reasons for discordance

Investigation of the reasons for the discordance observed in AGHI risk identification through FHx and genetic screening is essential to assessing the promise of genetic screening. The potential reasons for discordance are varied and include: (i) the participant has a truly negative family history of disease, (ii) the family health history intake assessment is flawed, or (iii) the family health history is unknown or was unreported by the participant. If this discordance is best explained by inadequate FHx intake, for example, then improvements in FHx processes might offer greater promise for optimizing identification of increased inherited disease risk. To investigate the reasons for this discordance, we designed a qualitative study of AGHI participants for whom FHx intake and genetic screening was discordant, as part of UAB's site-specific ELSI study for participation in the NIH eMERGE network (IRB 170303004).

Methods

Of the 90 AGHI participants with discordant risk elevation identified through FHx vs. genetic testing who had consented to re-contact, 16 agreed to participate in structured interviews. Interviews were conducted using Zoom software and lasted approximately 30 min. The full Qualitative Interview Guide can be seen in Fig. 1. All interviews were recorded, and transcribed by a professional transcriptionist under a confidentiality agreement. Qualitative content analysis, based on methods described in Schreier,[25] was conducted using NVivo software. Common themes were identified in the transcripts to provide definitions and

Table 2. Associated phenotypes and rate of high-risk personal or family history reported.

Phenotype	# with corroborating history/total # variants identified (%)
All cancer/tumour predisposition phenotypes	18/38 (47%)
Hereditary breast and ovarian cancer	13/21 (62%)
Lynch syndrome	4/9 (44%)
MUTYH-associated polyposis	0/5[a] (0%)
Multiple endocrine neoplasia, type 2/familial medullary thyroid cancer	1/2 (50%)
Hereditary paraganglioma–pheochromocytoma syndrome	0/1 (0%)
All cardiovascular phenotypes	15/41 (37%)
Cardiomyopathy	4/24 (17%)
Familial hypercholesterolaemia	9/11 (82%)
Arrhythmia	2/6 (33%)
Other phenotype: malignant hyperthermia	1/10 (10%)

[a]Includes 4 heterozygous results.

We are conducting a study examining how well 'Family Health History 'intake forms capture information, and how this history relates to your understanding of genetic testing results. We would like to discuss with you today your experience in filling out your family health history for AGHI as well as your experience with AGHI test results.

1. Can you describe your results from the AGHI in your own words?
    a. What did your AGHI result tell you about your health?
    b. What did your AGHI result tell you about the health of your family members?
    c. Was this genomic result new information for you, or did you already know about it prior to receiving it from the AGHI?
2. How would you rate your knowledge of your family health history (relatives who have been diagnosed with different diseases/health problems)?
    a. Is health information for relatives on one or both sides of your family unknown or unavailable to you? Why is this this case?

When you enrolled in AGHI, you filled out a questionnaire about your personal and family health history. I'm now going to ask you a few questions about that form.

**If the participant does not recall filling out the questionnaire or specific information about it, move onto the next section.*

3. What was your understanding of the reason for filling out this questionnaire and sharing personal and family health information with AGHI?
4. Do you recall having any problems filling out the questionnaire (instructions were not clear, not enough room, etc.)?
5. Were you able to include all of the family history information you wanted the study to know about? *(might be worded differently depending on answer to reason question)*
    a. If no, what additional information would you like the form to have captured about you or your family? *(or other similar follow-up question that reflects answer to reason question)*
6. Please tell me about the quality of your family relationships and what knowledge and sharing amongst family members is like?
7. Tell me about any adoption in your family.
8. Did you talk to anyone about your family history prior to completing the questionnaire?
9. Was the family history collection process clear?
10. Did you need any help filling the questionnaire out?
11. Have you talked to any of your family members about your AGHI results?
    a. If Yes...
        i. Which family members did you talk with? *We specifically would like to know how they are related to the interviewee (mother, sister, paternal aunt, etc)?*
        ii. Why did you decide to share your results with this person/these people? *(looking for motivations, what they were hoping to get from the interaction)*
        iii. Did this/these family members "do anything" based on hearing about your results? *(e.g., receive genetic testing, additional medical screenings, etc.)*
        iv. After getting your results, did you talk to relatives to gather more information about your family history?
            1. If Yes: Did you learn new information about your family history that you didn't know from these conversations?
    b. If No…
        i. Are there any reasons why you did not talk with your relatives about your AGHI results?

Now I am going to ask you some more questions about your personal and family history related to your AGHI result. There may be questions you don't know the answer to and that is ok. Answer them to the best of your knowledge.

12. Have you ever been diagnosed with [disease]? *([disease] filled in based on the disease associated with the positive result received)*
    a. If Yes...
        i. How old were you when you were diagnosed?
        ii. Was your diagnosis before or after you signed up for AGHI?
13. Have any of your family members ever been diagnosed with [disease]?
    a. If Yes...
        i. Who are those relatives? How are they related to you *(type of relationship, side of family, half/full sibling, etc)*?
        ii. How old were they when they were diagnosed?
        iii. Were the diagnoses before or after you signed up for AGHI?
        iv. Did you know about the diagnoses when you signed up for AGHI?
    b. *(If answered previously that they don't know any information about their family history)* Just to confirm, you are not aware of any biological relatives that have been diagnosed with [disease]?

Reconcile reported personal and family history from questionnaire and interview. Note whether there are any discrepancies (information given in one but not the other). For information listed on the enrollment questionnaire but not in the interview, continue to question 9. For information provided during the interview but not on the enrollment questionnaire, continue to question 10.

14. On the questionnaire you filled out when you signed up for AGHI, you told us that you have a [relative type] with [disease] diagnosed at [age]. I don't think you have mentioned this relative today. Was this someone you have already told me about or was that someone else?
15. Today you shared about a [relative type] with [disease] diagnosed at [age]. You did not list this person on the questionnaire you filled out when you signed up for AGHI. Do you know why this relative was not listed on the enrollment questionnaire?

Fig. 1. Qualitative interview guide.

details of the most prominent themes provided by the participants' responses.

Two themes arose across the interviews: (i) Family health history knowledge is multifactorial, and (ii) Communication among families regarding screening results was intended for proactive measures to be taken. No themes arose suggestive of ways to rectify discordance between family health history intake and genetic screening results through intake process.

Limitations

Saturation was not reached on some items, which may have been clarified with additional interviews. However, since our focus was solely on AGHI participants with discordant risk identified through FHx and genetic screening, further recruitment was not possible. Items for which saturation was not reached included: (i) whether participants intentionally talked to their family about their family health history prior to participation, (ii) whether they acted on their results, and (iii) whether they gathered additional family health history information after receiving their results.

Results

Theme 1: Family health history knowledge is multifactorial Participants were asked about their personal family health history knowledge, their familial relationships and knowledge sharing within their family. There were a variety of levels of knowledge and understanding of FHx, however nearly all participants had at least some knowledge of their family history. Several factors impacted participants' family health history knowledge and sharing. People with larger families, those who were adopted or had estrangement or divorce in their family, and those whose family did not share openly about medical issues due to age or cultural norms tended to have less knowledge of their FHx. People with medical/health background, people who were more inquisitive and asked more questions related to family history, and people whose family had more serious medical issues were more informed and tended to have talked to family previous to participation in the AGHI.

Participants indicated that they had very few difficulties filling out the family health history questionnaire (they were asked to talk about whether the instructions were clear, whether they had enough room to write, and whether they were able to include all the information they wanted the study to know about). Difficulties noted were primarily related to being unsure of the information they were asked to provide, for example if the participants had a nontypical family situation such as being adopted, having a mother who was adopted, or experiencing familial estrangement (Table 3).

Theme 2: Communication among families regarding screening results was intended for proactive measures to be taken Whether or not participants discussed their genomic results with their family members or gathered additional family health history after receiving their results depended largely on the results they obtained. Participants talked to family about results more frequently if their genomic results were concerning or novel. Participants did not report intentionally gathering information to expand their family health history knowledge, external to improving their understanding of their genomic results. Participants spoke mainly with immediate family members/ people who were genetically linked (e.g. their children or parents). They also tended to speak to health care providers in their family (e.g. nurses) about their results. When asked why they had these conversations, participants explained that they wanted to help protect the people they cared about.

Most importantly, themes for participant discussion did not centre around deficiencies in the family health history intake process, or rectifiable problems in family communication. Participants found the family health history form to be clear and sufficient. Evidence from this investigation does not suggest ways in which the family health history form could be improved to better capture information. Participants cited

Table 3. Exemplar and contradicting quotes.

Exemplar quote	Participant number
Theme 1: Family health history knowledge is multifactorial	
"Well, my kids, of course. I—I, you know, would rate higher. But my siblings and my parents are somewhat, um, I won't say evasive, but they only want to give you small bits and pieces of what's goin' on."	14
"I'm Asian, so unlike American families it's difficult for Asian kids to educate the parents. They don't take their kids as PhD or doctors. They take you as my daughter or my son. […] But in general, I think, Asian families, have different culture to what we have in the West."	11
"Um, good. There is a branch of the family I don't know much about because the—my grandmother divorced my biological grandfather."	6
"…since my mom was adopted, I think at the time there wasn't—like I didn't really know what to put."	7
"I learned a lot by asking questions"	16
Theme 2: Communication among families regarding screening results was intended for proactive measures to be taken	
"Well, because, like I said, we've all always felt like sitting ducks. And so if there were something that we could do to prevent, you know, having these cancers, I wanted them to be sure to be aware. And if they weren't even willing—I mean, I put the information in their hands. Um, it was up to them to follow up. And some of them did."	10
"I think she wanted to make sure that our kids definitely were, um—were screened for any problems they might have. Um, and if they happen to test positive for this, then they would know the proper precautions to take. And not only our kids, but my brother and sister and, um—and cousins. We were just trying to make the—the information available as widely disseminated as we could because, ah, information is power, right?"	3
"…in the case of my daughter, it's—it's, you know, really important that she know since it might impact her health. And sharing it with my wife, of course, we just share information about everything. So it was just a matter of course to do that."	5
"So that, you know, it's preventable, especially for the next generation. And, you know, their techniques of filtering genes. And ah—and if they get colonoscopies early on, you know, there's more that can be done. Or Pap smears or whatever, you know, depending on who they are."	15

having a large family, adoption (self and parent), estrangement/divorce, as well as race and generation-based impacts on family health history-based communication, knowledge and sharing as the greatest challenges for communication of health risks. These challenges are not rectifiable through the family health history intake process.

Conclusion

Based on the information gathered we do not see indication that the discordance between inherited disease risk identified via family health history and genomic testing is rectifiable through modifications to family health history intake forms. It appears that genomic screening can add to our assessment of risk over and above FHx, in a number of circumstances: First, in the absence of a robust family health history and/or in the case of conditions with reduced penetrance, genetic screening may provide valuable insight, unobtainable by other means, into an individual's risk, a conclusion consistent with the desired outcomes sought from genetic screening by, for example, adopted persons.[5,6]

The results of this combined study suggest that genetic screening may provide valuable inherited disease risk information even for those who have full access to family health history. Our study identifies cardiomyopathy, arrhythmia, and malignant hypothermia as conditions for which discordance between genetic screening and traditional FHx was greatest, and therefore areas where genetic screening offers great promise. These findings, however, reflect a limited scope of testing of variants associated with highly penetrant, highly pathological conditions which are often asymptomatic for long periods of time and for which effective medical intervention is available to cure or significantly mitigate the pathology in question (i.e. the ACMG criteria for investigation of secondary findings, which informed the AGHI screening panel).

Further research is needed to identify other conditions where genetic screening might add similar value outside the limited scope just described. Similar limitations apply to identification of areas wherein genetic screening can add nuance to inherited disease risk identified through traditional FHx (e.g. distinguishing type of cardiac risk and thus informing health management and prevention). It is our hope that the findings we present here can stimulate exploration of genetic screening value beyond these limited initial categories of disease–gene associations.

We conclude on the basis of our data that it appears risk assessment will be most accurate when family history and genetic screening are combined. The challenge with this approach is that genetic testing is a complex process offered only in specific settings, while family history is widely underutilized due to the difficulty of collecting and analysing the information.[26] The ideal scenario would include the availability of both genetic screening and a complete, accurate family health history, with each type of information potentially providing additional context for the other. Further research is required to determine if this pattern of concordance/discordance is retained in other populations, and how to most effectively incorporate genetic testing into family health history screening.

Supplementary material

Supplementary material is available at *Family Practice* online.

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Ethical approval

This study was reviewed and approved by the University of Alabama, Birmingham Institutional Review Board (IRB# 170303004).

Conflict of interest

Bruce Korf: consulting or advisory role: Springworks, AstraZeneca, Genome Medical, Envision Genomics, and Accolade; research funding: Novartis; patents, royalties: patent application related to treatment of neurofibromatosis type 1; travel, accommodations, and expenses: Springworks and AstraZeneca. Lori Orlando has an ownership interest in MeTree.

Prior presentation

To the ELSI working group of the NHGRI eMERGE Network (2022).

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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