Genomic Medicine 4

Family health history: underused for actionable risk assessment

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Family health history (FHH) is the most useful means of assessing risk for common chronic diseases. The odds ratio for risk of developing disease with a positive FHH is frequently greater than 2, and actions can be taken to mitigate risk by adhering to screening guidelines, genetic counselling, genetic risk testing, and other screening methods. Challenges to the routine acquisition of FHH include constraints on provider time to collect data and the difficulty in accessing risk calculators. Disease-specific and broader risk assessment software platforms have been developed, many with clinical decision support and informatics interoperability, but few access patient information directly. Software that allows integration of FHH with the electronic medical record and clinical decision support capabilities has provided solutions to many of these challenges. Patient facing, electronic medical record, and web-enabled FHH platforms have been developed, and can provide greater identification of risk compared with conventional FHH ascertainment in primary care. FHH, along with cascade screening, can be an important component of population health management approaches to overall reduction of risk.

Introduction

A detailed family health history (FHH) is the most useful tool for risk assessment for common chronic diseases. The relative risks and odds ratios (ORs) for various cancers, stroke, type 2 diabetes, and cardiovascular diseases exceed 2 for people with an affected first degree relative, and exceed 4 for many of these diseases if there is more than one affected first degree relative.[1] Although the Human Genome Project, genome-wide association studies, genome sequencing, and polygenic risk scores all portend a similar ability, FHH has remained the gold standard for risk assessment. The goals of precision health care and the capture and use of a high quality FHH are highly aligned. Precision health care aims to gather environmental, molecular, and social information from a person to make decisions that are tailored to that individual. FHH contains information relevant to these spheres of risk. Furthermore, FHH can help with decisions early in life to mitigate risks of diseases that might present later, such as adoption of better dietary habits in the face of the risk of heart disease or of diabetes. An FHH can be added to and passed on to future generations, providing a foundational risk profile for immediate family and their progeny for generations to come.

	Risk algorithm based on family health history only	Risk algorithms that include family health history
Hereditary breast and ovarian cancer	✓	..
Hereditary non-polyposis colon cancer (Lynch syndrome)	✓	..
Alpha-1-antitrypsin deficiency	✓	..
Diabetes type 2	..	✓
Abdominal aortic aneurysm	..	✓
Coronary artery disease	..	✓
Haemochromatosis	✓	..
Maturity onset diabetes of the young	..	✓
Osteoporosis	..	✓
Asthma	..	✓
Melanoma	..	✓
Prostate cancer	..	✓
Age-related macular degeneration	..	✓

Adapted from Orlando et al.[4]

Table 1: **Examples of conditions for which family health history and health risk assessments are useful**

FHH and health risk assessment

In 1961, Kannel and colleagues[2] first used the term "factors of risk," indicating that male sex, diabetes, high serum cholesterol, high blood pressure, and a positive FHH of early heart disease could inform a model for predicting heart disease, which is now widely known as the Framingham Risk Score.[3] These same risk factors have now become the basis for health risk assessments (HRAs) for heart disease. HRAs are an essential component of establishing an individual's risk for developing common chronic diseases (table 1)[4] allowing providers to tailor preventive care, screening, and follow-on testing of risk, with the goal of health maintenance. The focus on disease risk mitigation is an approach some have called precision health.[5] Strategic and individualised health care plans can be developed with the aid of HRAs that balance effectiveness of the interventions to mitigate risk with risk of the disease development if they are not done. When summed across a group of individuals, such as in a health plan or health-care delivery system, HRA information provides the basis for population health management.

Even with the proliferation of genome-wide association study findings, and polygenic risk scores,[6] FHH remains

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the strongest predictor of disease risk for some conditions and is recommended as the primary component of risk assessment in many global guidelines.[7–9] No studies have yet thoroughly compared the value of FHH and polygenic risk scores or their overlap and complementarity.[10] For hereditary cancer syndromes, FHH is the only predictor (and thus the only component of the HRA). An example of the effect of FHH on disease risk can be illustrated with type 2 diabetes, in which having a first degree relative (parent or child) with the disease increases an individual's risk from an average of 3·2% to 14·3%.[11] Exclusion of FHH can lead to missing those at highest risk for developing a condition. Many HRAs for chronic obstructive pulmonary disease ask about environmental exposures (such as smoking and asbestos), but do not ask about FHH; however, patients with alpha-1-antitrypsin deficiency, an inherited condition, are at the highest risk of developing chronic obstructive pulmonary disease even without an environmental exposure.[12] The ORs for many common disease risks as derived from FHH are much higher (and more actionable) than those obtained for carrying the risk allele from genome-wide association studies. Qureshi and colleagues[13] reported the potential to identify pre-symptomatic individuals at elevated risk for common, chronic diseases and activate them to modify their risks, presenting an enormous opportunity to improve public health by implementing risk-based screening and prevention strategies.

In addition to being highly predictive, FHH also serves as the basis for several evidence-based guidelines[7–9] that not only indicate the disease risk associated with a given combination of affected relatives, but also risk-managing actions to take. For example, the National Comprehensive Cancer Network's guidelines for breast and ovarian cancer recommend BRCA testing if an individual's first-degree relative (parent or child) developed breast cancer at age 45 years or younger.[14] Another example is abdominal aortic aneurysm screening: if an individual has a relative with the condition, then screening beginning at age 50 is recommended.[15,16]

FHH is therefore a key data element in HRAs that is both highly predictive and actionable in combination with other data elements and by itself. Unfortunately, FHH is often hard to obtain. Individuals often do not know much about their relatives' health and what they do know is often piecemeal or could be inaccurate,[17] which leads to one of the most informative data elements in HRAs also being one of the more difficult to obtain; however, research teams around the world have been developing solutions to obtaining a robust and accurate FHH and helping providers and patients take action from the data that is gathered.

In 2002, the US Centers for Disease Control launched the Family History Public Health Initiative,[18] to invigorate the use of FHH for risk stratification. One of the stated goals was to develop tools to enhance FHH collection and to investigate whether FHH-based strategies work in practice. Because primary care providers account for most care encounters in the USA they are a natural choice as partners in the implementation of FHH into care delivery and medical decision making.

FHH assessments have clearly been shown to identify people at higher risk for common chronic disease, enabling pre-emptive and preventive steps, including lifestyle changes, health screenings, testing, and early treatment as appropriate.[19] However, although FHH is a standard component of the medical interview and professional guidelines recommend screening strategies based upon FHH, its widespread adoption is hindered by three major barriers: reliance on provider ascertainment of data during a clinical visit, the difficulty for health-care providers to access a clinically integrated centralised repository of risk calculators in the context of a time-limited clinic visit (despite the growth of web and available application programming interfaces); and paucity of electronic health record (EHR)-integrated clinical guidance for interpretation and use of FHH information.

Using FHH tools versus conventional acquisition of FHH

FHH is underused by practitioners and represents a missed opportunity for risk stratification.[20] A systematic review[21] found a 46–78% improvement in data recording by FHH tools as compared with the use of standard practice. FHH tools show excellent concordance with structured pedigree interviews and the gold standard three-generation pedigree.[22] In a study[23] of 1124 primary care patients, medical record documentation was insufficient in two-thirds of charts for FHH assessment of six common diseases, and 23% had no evidence of risk in their medical record yet had a moderate or strong risk for at least one disease as assessed by the Family Healthware tool.[23]

FHH collection, analysis, and risk stratification can be done efficiently and effectively using various software platforms that have the potential to overcome the barriers created by a reliance on physicians to gather, record, and analyse FHH. Implementation of automated FHH linked to clinical decision support (CDS) is feasible in the community setting. Early experience using the MeTree FHH software platform showed that the mean completion time by 1184 primary care patients was 27 minutes.[24,25] Given the time commitment required to capture a complete FHH, our own work and others suggest that patients, not physicians, need to serve as the main locus for data input.

Clinical validity and clinical utility of FHH

If FHH is to be collected more systematically and patients are to become a major source of data entry for their FHH, then questions of analytic validity; clinical validity; clinical utility; and ethical, legal, and social issues should be examined. A useful framework for examining these

questions is the analytic validity, clinical validity, clinical utility, ethical issues (ACCE) framework.[26] Initially developed as a way for policy makers and clinicians to investigate genetic testing development and value, this framework also can be applied to evaluation of FHH risk assessment platforms.[27]

Analytic validity

FHH acquired through genetic counsellor interviews has been considered the gold standard for FHH data quality, but patient facing FHH risk assessment platforms are of equal or better quality.[21,28,29] In addition, probands have fairly high accuracy in the reporting of common medical conditions (eg, coronary heart disease, diabetes) of family members when compared with the family members' own report.[30] Compared with routine clinical care either in paper charts or the EHR, patient-facing FHH platforms routinely perform much better in data completeness and accuracy.[28,31,32]

Clinical validity

To engage clinicians in systematic collection and assessment of FHH, the usefulness of FHH in predicting disease needs to be established, which is challenging as studies vary in their definition of a positive FHH and long-term outcome studies are few. For example, having a parent with diabetes results in development of diabetes in 16–47% of people.[33,34] Such a wide range puts into question the sensitivity of FHH in establishing disease risk. More, large longitudinal epidemiologic studies among healthy populations need to be done to understand the true risk that a positive FHH conveys and how it should be used for risk stratification.[35–38] For the time being, FHH risk platforms should focus on aligning with clinical guidelines to provide a consistent framework for understanding risk.

Clinical utility

FHH platforms routinely identify a noteworthy proportion of the population that meet guideline criteria for increased risk of specific conditions (eg, specific cancers, hereditary cancer, or cardiac syndromes), most of which had not been previously identified through routine care.[13,28,39,40] In studies with MeTree,[41,42] 44% of 1144 primary care patients met guideline criteria for non-routine risk management for five studied conditions and 26% of the population met criteria for referral to genetic counselling for potential hereditary risk.[39] Another FHH software platform, the Health Heritage risk assessment, reported similar results with 42% of participants identified as at increased risk.[28] The third major FHH risk assessment platform that has been evaluated in clinical trials, Family Healthware, identified 34% of participants at strong or moderate risk for at least one cancer.[43] Only 17–43% of participants had received appropriate screening before the risk assessment and 3% had received recommended genetic counselling.[43] These rates are in line with the experience of other FHH-based risk assessment platforms.[29,44]

See Online for appendix

Evidence suggests that identification of FHH-based risk leads to patient and provider changes in behaviour both in terms of risk-mitigating lifestyle changes, and ordering and receiving genetic counselling and genetic testing.[13,45,46] We have also seen that there is wide uptake of such interventions across a diversity of populations.[47] MeTree was implemented across four diverse health systems (rural, urban, academic, private) across the USA with uptake by a diverse population including 22% ethnic minority and 25% with less than a college education.[47]

What remains to be done is a complete economic model to understand the long-term financial and health effect of systematicallly assessing risk with patient-facing digital platforms on disease prevention and earlier disease identification at a population level. Such an analysis is needed to achieve payer and institutional buy-in. There have been models of risk-based screening for colon cancer and breast cancer showing that population-level implementation of these strategies are cost-effective, reduce overdiagnosis and adverse events, and maintain the benefits of screening.[48–51] These models need to be further expanded to address a wider range of conditions in which FHH-based risk stratification can direct healthcare services most effectively, how digital platforms can assist in that process, and the long-term effect of such risk assessments.

Integration of FHH platforms with information technology systems

Challenges to gathering and synthesising FHH face patients, providers, and health systems. On the patient and provider side, these challenges include paucity of knowledge about family members' health conditions, underappreciation of the importance of family members' health to individual risk, the complexity of translating FHH into an actionable risk management plan, the time constraints of traditional clinical visits, inadequate tools for facilitating data collection and data storage, and paucity of adequate CDS.[17,52–57] Although the creation of digital tools and EHRs generated initial optimism for overcoming these barriers, there has been little progress. In fact, the EHR has been shown to decrease the quantity of FHH collected.[58]

The ideal FHH platform

In 2008, the American Health Information Community developed data standards for obtaining an adequate FHH for risk assessment.[59] In 2014, deHoog[58] outlined the ideal features for an FHH programme: computerised, patient administered, easy to use, collects all data necessary for risk stratification, updateable, has integrated risk algorithms and evidence-based CDS, and can communicate with the EHR (appendix). By comparison, most of the major USA EHR vendors are not patient administered, not easy to use, do not collect all of the

	Disease categories	Number of diseases	Decision support provided to	Supports HL7 inter-operability	Availability to patients	Affiliated with genetic testing company
Ancestry Health	Several categories	450	Patient	No	No	✓
CancerGene Connect	Cancer	112	Clinician	✓	Through health-care provider	✓
CancerIQ Self-Assessment	Cancer	30	Clinician	✓	Through health-care provider	No
CRA Health	Cancer	18	Clinician	✓	Through health-care provider	No
Family Healthware	Major diseases	6	Patient	No	Available to public for US$9·99 per month	No
Health Heritage	Several categories	47	Patient	✓	Through health-care provider	✓
Inherited Health	Several categories	282	Patient	No	Available to the public for $39·95 per year	✓
Invitae FHx Tool	Cancer	24	Clinician	✓	Through health-care provider	✓
ItRunsInMyFamily	Cancer	97	Patient	✓	Available to public for free	No
MeTree	Several categories	123	Clinician and patient	✓	Research study access only	No
My Family Health Portrait	Several categories	87	Patient	✓	Available to public for free	No
MyFamilyHealth	Major diseases	15	Patient	No	Available for free. Not fully functional	No
MyLegacy	Major diseases	12	Clinician and patient	✓	Through health-care provider	✓
Myriad FHx tool	Cancer	26	Patient	No	Available to public for free	✓
Our Family Health	Several categories	533	None	No	Through health-care provider	No
Progeny FHQ	Several categories	387	Clinician	✓	Through health-care provider	✓
VICKY	Major diseases	20	None	✓	Research study access only	No

Adapted from Welch et al.[67]

Table 2: **Risk assessment platform identification of elevated risk populations**

necessary data, and do not have integrated risk algorithms or CDS. For example, only a few FHH conditions are represented as discrete data elements in the family history section of the EHR. Most health systems allow providers to choose 10–20 conditions as part of their FHH package. Conditions not on the list should be entered as free text. In addition, there are no data fields to record age of death and cause of death of family members.

For providers, integrated risk algorithms, CDS, and communication with EHRs are essential. Without these features, FHH-based risk assessment cannot be fully incorporated into the normal clinical workflow and will continue to be underused.[47] Left to their own judgment, clinicians have been shown to underestimate and overestimate risk.[60,61] Standardised risk algorithms are essential for providing evidence-guided risk assessment. Risk algorithms are necessary to find out whether a patient meets criteria for many evidence-based risk management strategies. The Tyrer-Cuzick breast cancer risk calculator provides information on 10-year and lifetime risk of breast cancer.[62] This algorithm identifies those who warrant breast MRIs as an adjunct to annual mammogram for breast cancer surveillance[63] but the calculation is much too complex to perform without a computer and this complexity decreases uptake in busy clinical environments where providers will not exit the EHR workflow to do the calculations.[64] Even those algorithms that do not include risk calculators, such as the National Comprehensive Cancer Network's guidelines for identifying patients who warrant testing for hereditary cancer syndromes, are long, complex, and cover multiple permutations of family members, disease, and age of onset.[65] In real-world clinical practice, where physicians have 10 min of face-to-face time with their patients, 3 min to go to an external website and manually enter patient data to get back a risk score that is not tied to a specific actionable care plan is 3 min too long.[66] Moreover, evidence-based guidelines exist for risk assessment on almost 50 different hereditary and common complex conditions. Although many of these are inter-related, particularly those like breast cancer that can increase risk not only for the condition itself, but also for other cancers when part of a hereditary cancer syndrome (eg, Hereditary Breast and Ovarian Cancer Syndrome), systematically assessing risk for every patient across all these conditions without an automated and systematic process integrated within the EHR is not feasible.

Emerging technologies could address these challenges. Investigators and developers have created new software solutions to facilitate FHH collection and analysis at an increasing rate (see table 2 for a detailed comparison of the most prevalent USA-based tools and the Genomic data toolkit for a global but less detailed comparison), though many of these were either specifically developed to complement services offered by a company or were purchased by companies to assist them in driving demand for their product.[67,68] For example, Health Heritage[28] (developed at University of Virginia, VA, USA) was purchased by NantHealth, and Invitae (a genetic testing company) acquired CancerGene

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Connect,[69] an FHH platform developed at the University of Texas Southwestern (TX, USA). Advances in informatics data standards, specifically the SMART on FHIR specifications that have been adopted by most of the major EHR vendors, including Epic, Cerner, and Athenahealth, could help to fill the gap in primary care and cancer clinics, where FHH is most successfully addressed.[70] This data standard, which addresses the most difficult deHoog[58] criterion of communication with EHRs allows third party software systems, such as an FHH platform, to push and pull data from a connected EHR and to permit single sign-on access for patients and providers that minimises interruptions in workflow. The data standard also allows software developers to do what they can do much better than the EHR vendors—ie, leverage graphical user interfaces for usability, facilitate patient entry of data, and visualise data to promote knowledge assimilation and CDS for providers. Integration of software with EHRs is picking up speed, but regulations such as the EU General Data Protection Regulation could place some limitations on its use. Patient-facing software applications will probably be regulated, at least in the EU, on a country by country basis. How the regulations will affect the use of FHH software is unclear.

In the optimal scenario, FHH data collection is removed from the actual clinic visit. Patients, empowered and educated on how to gather high quality and thorough family history information, confer with relatives then access a patient-facing platform where they enter their family data. Providing up-front patient education about FHH and what information is important to collect is crucial, and has been shown to improve patients' ability to provide complete and accurate information that can have an effect on the conditions they are identified as being at risk for.[71] After patients enter their FHH data, the platform automates running of risk algorithms and provides CDS to both patient (in real time) and provider (at the point of care) to facilitate shared decision making. As a proof of concept for this model, MeTree was integrated with the Epic EHR at Duke University via a SMART on FHIR connection. This successful demonstration, funded by the National Human Genome Research Institute's Implementing Genomics In Practice (IGNITE) network,[72] allows patients to access the FHH platform through a single sign-on link in the patient portal, pulls relevant data into the platform to prepopulate fields, and generates a graphical dashboard and CDS recommendations for providers within the patient's chart. With this final hurdle addressed, the potential for technological solutions to meet the deHoog criteria,[58] and revolutionise systematic risk assessment is at hand.

FHH and population health

If applied across the general population, systematic FHH-based risk assessment has the potential to have a substantial effect on population health management. Up to 44% of people meet criteria for increased risk for at least one hereditary condition based on current guidelines, so the potential for impact on health is huge.[40] Scaled to a population, FHH becomes a means of assessing the true risk and potential costs that a health system might use to better manage its financial risk. When multiplied to potentially affected family members, the effect becomes even greater.

Although FHH is recognised as a key driver of many chronic conditions, its use as a means of risk identification has not been optimised with many at-risk individuals remaining unidentified and few having collected and used their FHH in a meaningful way.[73] FHH of diabetes is estimated to be the main cause of more than 15 million diabetic and pre-diabetic cases in the USA, but more than 1·4 million of these remain undiagnosed.[74] Similarly, Lynch syndrome affects an estimated 1 in 370 Americans, but less than 1·2% of these have been diagnosed.[75] In the current system, risk assessment is non-systematic and health care is provider-driven and dependent on the patient presenting to the health system, leading to low identification rates, non-guideline concordant care, and racial and socioeconomic disparities in identification and referral rates.[76–78] Among first-degree family members of people with premature coronary heart disease in EUROASPIRE II,[79] screening for coronary risk factors had only occurred in 11·1% of siblings and 5·6% of children despite the prevalence of coronary heart disease risk factors. In the case of familial hypercholesterolaemia and severe dyslipidaemia, identification rates in the USA are fairly high (80%) but appropriate treatment with high-intensity statins are low (30%).[80] Multiple guidelines recommend genetic counselling before genetic testing as genetic counselling has been shown to lead to greater understanding of genetic testing and higher satisfaction with the process, yet only 36·8% of BRCA-tested patients receive such counselling.[81] The most frequently cited reason for not seeing a genetic counsellor was absence of physician recommendation. In addition, our current processes lead to racial and socioeconomic disparities in identification rates and care management with ethnic minorities and less educated patients being significantly less likely to receive testing, both as a part of a prevention plan and for those already affected by cancer.[82,83]

Use of FHH-based risk assessment to drive identification of index cases and successive cascade screening for inherited conditions (eg, familial hypercholesterolaemia, hereditary breast cancer, and ovarian cancer) has the potential to be a valuable strategy to maximise the potential for FHH to affect individuals, families, and populations. The value of cascade screening in affecting population health, while remaining cost-effective, has been shown in many countries around the world.[82,84–86] The Netherlands familial hypercholesterolaemia programme is one of the best examples of such a population-wide programme. Familial hypercholesterolaemia leads to a 3–4 times increased risk of

coronary heart disease compared with unaffected people, and coronary heart disease events typically occur up to one decade earlier than in unaffected people.[87] In the 20 years since the Netherlands programme began, they have identified more than 26 000 mutation carriers through national cascade screening efforts. Rates of appropriate treatment for familial hypercholesterolaemia (ie, statin therapy) increased from 39% to 93% within the first year after diagnosis as a result of these efforts.[85]

In addition, health care cannot remain in the model of waiting for the patient to come to the system. In the same way in which cascade genetic testing moves from one affected person to an ever-expanding ripple effect within their families to identify additional cases, there is an opportunity to apply these same concepts to risk assessment, leveraging family connections to maximise effect. Through application of social network technologies, there is the potential to reach more people through their family relationship networks. In addition to reaching more people, families would be further improving the accuracy of the FHH data captured and the assessment of risk for themselves and their family members. These principles of leveraging social networks are already being applied in genealogic research and are well established in the family systems model.[88]

Future directions

FHH has the potential to become a key platform for risk assessment, precision health care, and population health management. Genome sequence data combined with FHH, lifestyle, and environmental data will provide the most robust means to identify individuals at risk and clear actions to reduce the risk of common complex diseases. With the advent of global digitisation of medicine and patient and consumer empowerment, health systems around the globe should adopt patient-facing FHH applications and promote the sharing of information across families to provide not only an unprecedented opportunity to mobilise large scale prevention and screening strategies, but also a rich data resource to enable discovery genomics research on inherited factors contributing to complex disease. The community working on novel FHH approaches will need to develop standards for acquisition of data and its storage for longitudinal use, increasingly robust interfaces with EHRs where they are used, and research programmes to optimise risk algorithms using large scale FHH data combined with genomic and environmental data.

Contributors

All authors were involved in conception, writing, and editing of this manuscript. All have reviewed and approved the final version.

Declaration of interests

The authors are co-founders of a company that has licensed MeTree from Duke University.

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