Family Medicine & Medical Science Research

Henrich and Orlando, Fam Med Med Sci Res 2015, 4:5
DOI: 10.4172/2327-4972.1000185

Mini Review Open Access

Family Health History: An Entry for Personalized Medical Practice in Primary Care

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Introduction

The successful practice of personalized medicine in primary care depends upon understanding a patient's individual disease risk and anticipating the best course of treatment with the goal of maintaining good health. A personalized disease risk assessment leads to recommendations for evidence-based interventions that can delay/prevent disease onset or reduce the severity of disease. As the sophistication of medical diagnoses develops and new interventions become available, the value of collecting and analyzing family health history (FHH) for maintaining patient wellness by determining 'the right treatment, at the right time, for the right patient' is more apparent than ever. FHH remains underutilized in primary care, however, because of numerous barriers. Ironically, the introduction of genetic tests and genomic methods that identify carriers who might be vulnerable to a variety of medical conditions and diseases has simply raised the importance of collecting and utilizing FHH to guide patient management in primary care.

FHH is perhaps the most cost-effective and robust means to obtain information about a patient's disease risk [1-3]. A complete FHH includes the health information of a patient's blood-related first (parents, siblings, children) and second degree (half-siblings, aunts, uncles, grandparents) relatives over three generations. To be optimally useable for analysis, FHH will denote both affected and unaffected family members, the age of disease onset, disease severity, any recurrences, and cause of death [4]. Even partial FHH information can be useful; however, especially if two or more first or second degree relatives are affected from either the maternal or paternal side of a family, since two occurrences of a disease or condition within a lineage usually is sufficient to conclude that an elevated disease risk exists.

Family Health History: Its Collection and Use

Generally, actual risk assessment algorithms derived from FHH information vary for different diseases, especially when other factors, such as age of onset, severity, recurrence, and environmental risk factors are known to be involved. For some diseases, FHH-based risk is described primarily for first degree relatives. In such cases, individual risk is elevated substantially if an immediate (first degree) family member is affected, and the additional risk revealed by affected second degree relatives may not be necessary for generating additional recommendations, and/or treatment interventions, though this information could be valuable if a genetic test is contemplated. For assessing a patient's risk for developing diabetes mellitus, for example, having a first degree relative with type 2 diabetes significantly elevates personal risk (~2-5 fold), even without knowing exacerbating environmental risk factors and without information from more distant relatives [5]. While specific genetic variants (any structural change in the nucleotide sequence of DNA will be referred to as a variant in this mini review) that occur commonly in the human population have been associated with a risk for type 2 diabetes, FHH remains a more robust predictor of T2D risk than the presence of predisposing genetic variants [5,6]. For stroke, FHH is a well-established risk factor. According to one study, over 85% of strokes in persons less than 75 years old are concentrated in about 10% of all families, suggesting the risk-elevating effects of genetics and shared family environment [7]. If one or both parents of a patient had a stroke, a patient's risk for stroke or cardiovascular disease is significantly increased [8]. Such information offers a simple and effective form of triage for evaluating a patient's risk for stroke as well as possible interventions, including aggressive treatment of even modest hypertensive levels, which has been shown to reduce the risk of cardiovascular disease and stroke by one-fourth to one-third [9]. Several genetic associations have been tentatively made for a variety of specific types of stroke, precluding the utility of a simple genetic test for stroke risk [10]; the disease itself is heterogeneous in terms of cause and type, and these subtypes involve a variety of potential variants, none of which have been validated as predictors of stroke risk in the general population. As the relationship between specific types of stroke and predisposing genetic and environmental factors becomes more defined however, it is plausible that more precise diagnoses, preventive interventions, and treatments will be forthcoming.

Colorectal cancer (CRC) and breast/ovarian cancer (Br/OvCa) demonstrate the utility of gathering FHH for the patient population in a primary care practice as both cancers are relatively common; in the US, the combined lifetime incidence of these two forms of cancer is over 20% [11]. Between 30 and 40 percent of all US patients have a FHH indicative of an elevated lifetime risk for Br/OvCa or CRC (12 and references therein). A clinical study of FHH-based risk assessment among 1000+ primary care patients revealed that 47% had at least one relative who had been diagnosed with breast/ovarian cancer, 24% had one or more with CRC, and 2% had one or more with a hereditary cancer syndrome [12]. Even when not entirely prevented, early detection based on intensified screening is key for the successful treatment of these cancers when they occur: BrCa survival rate is 88% when treatment starts at Stage I; but only 15% when started at Stage IV [11]. Similarly, for CRC, five-year survival drops from 74% when diagnosed and treated in stage I to 28% in stage IIIc. Further, these cancers are preventable in many instances, with early screening, treatment, and/or intensified screening that is reimbursable and based on medical evidence.

Among the 20% or so of individuals who have a FHH for CRC, that is, a first degree relative or at least two second degree relatives on the same side of the family who developed polyps or CRC before age 60, lifetime incidence is over twice as high (16%) as in the general population (5-6%), and these odds are significantly higher than those for

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Received September 29, 2015; **Accepted** October 09, 2015; **Published** October 15, 2015

Citation: Henrich VC, Orlando LA (2015) Family Health History: An Entry for Personalized Medical Practice in Primary Care. Fam Med Med Sci Res 4: 185. doi:10.4172/2327-4972.1000185

a positive test result for any one of the genes associated with CRC [13]. For moderate to high risk patients, colonoscopies are recommended starting 10 years before the earliest age of diagnosis in the family (including the earliest detection of polyps), and no later than age 40; in fact, ~20% of patients diagnosed with an FHH-conferred risk develop polyps before the age of 50 [14]. For BrCa, the overall lifetime risk is about 12% in the general population, ranging from about 8% among women who have no FHH of breast cancer by age 40, to ~13% for those with a single first degree relative diagnosed with breast cancer , and ~20% for those who had two or more first degree relatives diagnosed with BrCa [15]. About 30% of all women have a FHH of BrCa, though ≤ 20% of these women (~ 6% of all women) are carriers of the BRCA1 or BRCA2 mutations [16]; mutation carriers have a BrCa lifetime risk of 50% or more). Importantly, women who have a FHH of breast/ovarian cancer usually are not carriers of these mutations, but lifetime BrCa risk is still twice as high for them as compared to those with no FHH [15]. A positive FHH by itself may lead to a recommendation for intensive MRI screening, genetic counseling to consider further genetic testing, and/or estrogen therapy [17,18].

FHH by itself cannot distinguish asymptomatic genetic variant carriers and noncarriers within a family. Therefore, a FHH for these cancers may point to a significant benefit to individuals who choose to undergo testing in order to learn their personal risk. Nevertheless, the likelihood of a positive test result for a clinically relevant variant of BRCA1/2 is low in the absence of a positive FHH. BRCA1/2 variants have been found in patients from smaller families with no FHH [19,20], though the high cancer risk seen among carriers of BRCA1/2 variants has prompted calls for community level screening programs [21].

A focus on identification of at-risk subjects for breast/ovarian and colorectal cancers based on FHH could be particularly beneficial for traditionally underserved populations in the US. For instance, the death rate for these cancers is significantly elevated in the African-American population compared to others, even though incidence is not. Cancer (all types) is far and away the leading cause of death between the ages of 45-54 (440 per 100,000; second is heart disease, 374 per 100,000) among African-Americans [13]. By reducing incidence through prevention and screening regimens that improve early detection, it has been argued that the costs of treatment and mortality rates could be reduced [22].

Given the proven value of FHH for disease risk assessment, efforts have been made in recent years to employ computational interfaces which allow patients to collect FHH from family members for a variety of diseases and conditions prior to an appointment. Numerous patient-facing tools which collect FHH information for several diseases have been introduced [23-28]. These tools enhance the value of FHH information because they prompt the patient to provide FHH for all of a patient's blood relatives, along with potentially important information such as age of disease onset among affected members, any recurrences, and when relevant, age/cause of death. Knowledge of unaffected family members is also important because it can refine the risk assessment further (moderate vs high), inform the practitioner and patient about other at risk family members who are still unaffected, and if a genetic test seems appropriate, identify other potential carriers (and noncarriers) within a family lineage. At least one tool additionally provides the physician and patient with a risk assessment for specific diseases, utilizing risk algorithms, based on epidemiological evidence such as described earlier for CRC and breast/ovarian cancer [12,28] and further, offers medical recommendations based on the results of risk stratification, for hereditary cancer syndromes, familial cancers, and deep vein thrombosis [27,28]. FHH collection and analysis tools promise to drive a transition in primary care practice towards a model in which disease risk assessment and prescribed treatment are increasingly tailored to the patient's personal history and FHH, with the goal of preventing, delaying, and minimizing the effects of disease and extending the patient's quality of life [29].

Obstacles to FHH usage in family practice

Despite the utility of FHH for assessing disease risk and offering recommendations to reduce risk in practice, only about 4% of patient records, in one study, had sufficient information to perform an assessment and to offer recommendations based on FHH suggesting the need for improved health provider education about the collection and use of FHH [30]. The existence of decision support substantially affected practitioner behavior as their referrals to a genetic counselor were made for about 14% of all patients, whereas GC referral had been almost nonexistent prior to the study and in a control practice. However, this still represents less than half of the 29% who had been recommended for genetic counseling based on the risk levels calculated by the tool. Moreover, less than a third of the referred patients actually met with a genetic counselor [31].

Practitioners themselves have cited barriers to the expanded use of FHH in the clinic: the physician's lack of time to collect and evaluate FHH, the need for periodic FHH updating by patients and consequent risk adjustment, the practitioner's reticence to discuss disease risk extensively with the patient and make altered recommendations based on FHH, uncertainty about the purpose of genetic counseling, the patient's lack of knowledge about her/his own FHH and the patient's own reluctance to communicate with family members and comply with recommendations arising from the analysis of FHH [32].

Educational intervention in conjunction with FHH compilation improves patient follow-up [33,34]. For those who face a FHH-based risk, however, the personalization of medical care will further require that community organizations are coordinated and networked to meet the patient's needs as they arise and provide education in light of an assessment that indicates elevated risk [29].

Merging FHH, genetics, and genomics in family practice

As noted, FHH analysis alone cannot distinguish genetic carriers and noncarriers among asymptomatic carriers, and cannot be used to interpret possible gender-specific or age-related disease patterns. Shared environmental factors that could affect FHH, such as lifestyle habits, nutrition, or exposures cannot be partitioned without more detailed information. Further, shared environmental factors can modify gene activity [35] or the community composition of intestinal micro biomes [36] to influence personal health; possible genetic differences, on the other hand, are most evident when one or more family members show a distinct response to the same environmental factor.

There are specific genotypes that are useful in family practice, such as known genetic variants that predict adverse drug responses (ADRs) to widely used pharmaceutical agents, including common analgesics, blood thinners, statins, and various psychoactive drugs. DNA sequencing of genes encoding proteins involved in drug uptake, transport, action, metabolism, and excretion frequently carry variants that could alter treatment for specific patients [37]. By extension, simply knowing about ADRs in other family members could provide useful information to the practitioner that suggests the benefit of genetic testing, and/or an alternative prescription for the treatment of a family member.

The genetic diagnosis of chronic diseases is considerably more

difficult than testing for drug response, because of the limited prevalence of specific risk-imposing variants in the general population, the modest impact of such variants on disease risk levels, the modulatory effects of 'second-site' genetic variants, and the importance of specific environmental factors or exposures to trigger or exacerbate a disease condition. The Factor V Leyden polymorphism is a mutation that causes an amino acid substitution in the sequence of a blood clotting factor, for example, and thereby, increases risk for deep vein thrombosis, though only about 10% of Leyden carriers actually develop DVT [38]. Other genetic variants of low or modest frequency in blood factor genes also show low penetrance features resembling those of the Leyden mutation [39,40]. Here, the value of collecting a patient's FHH for DVT is that it could indicate the desirability of genetic testing, and prompt recommendations based on the risks posed by oral contraceptive administration and unhealthy lifestyle choices in confirmed genetic carriers.

The perceived precision of well-defined genetic test results, which in specific instances, provide clear cut information , has driven the introduction of genetic test panels available directly to consumers, and in the process, has posed a challenge to medical practitioners struggling to evaluate and interpret this information. Commercial panels will assay a patient's genome for numerous commonly occurring genetic variants and offer the consumer an assessment of their personal risk for a variety of diseases and conditions, including various types of cancer, diabetes, cardiovascular and neurological diseases [41,42]. These tests mostly describe a class of variants, known as single nucleotide polymorphisms (SNPs), scattered over all 23 pairs of chromosomes and within and between the 30,000 or so genes in the human genome. SNPs have been described for about 12 million individual DNA base pairs whose location is enumerated in the Human Genome database based on their location among the 3 billion or so base pairs that comprise the genome and have been catalogued because they occur at a detectable frequency in human genomes [43]. SNPs are often not homogeneously or broadly distributed; many SNPs occur in specific subpopulations and do not appear in others, except upon admixture.

While the SNP commercial tests can be interesting and in specific instances, could be informative, their overall value for making medical decisions has not been established. The effects of specific SNP variants for a given disease risk are usually modest and often uncertain and the modulatory effects of environmental factors/exposures are not typically described or even known. For the practitioner, the problem extends beyond the test results themselves, by raising doubts about whether a patient's reaction to the results will lead to beneficial actions. In summary, while genomic panels identify specific genetic variants, they usually describe genotypes that remain poorly described in medical settings, for which little or no information exists about the disease mechanism involved, and with a method that cannot be used to detect variants which might be restricted to a family lineage (or a specific patient).

New Next Generation methods, through which a patient's entire genome is sequenced, and/or exome sequencing, wherein the gene coding regions within the genome are sequenced, enhances the search and discovery of the individual and familial variants responsible for disease and this approach is poised to supersede SNP-based genomic analysis. It has already established that every individual has a degree of 'personal genomics' [44]. Ironically, this expansion of genomic information heightens the need for FHH, as these lineage specific variants could have a significant impact on medical recommendations and tailoring precise and personalized treatments. Therefore, the complementary compilation of FHH and familial genomic information could become an essential prerequisite for achieving personalized medical practice in the future.

Summary and Conclusion

FHH provides important information concerning a patient's disease risk that leads to altered medical recommendations to patients with above average (moderate to high) risk for developing various chronic diseases. The ability to expand the use of FHH will depend upon the continued development of patient-faced FHH collection tools, improved education for both patients and practitioners, and a model of medical practice that is dialogue-driven and where the patient acts upon information and recommendations that follow from an assessment of the patient's inherent risks, potentially harmful exposures, and lifestyle choices. The advent of personal genomics, paradoxically, will further heighten the need for FHH information as a basis for bringing effective and precise treatment to the patient.

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