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The Family History: Reemergence of an Established Tool

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Introduction

There is a perception that the family history has played little if any role in the management of patients in an intensive care setting; the family history may be considered “noncontributory” in the context of caring for an acutely ill patient. The health care team is focused on stabilizing the patient and responding to acute often life threatening needs. To this end, patient evaluation is often restricted. The time honored primary survey prioritizes assessment “ABC” (Airway, Breathing, Circulation) and has been expanded to include D for Disability and E for Exposure. However, a growing body of knowledge in human genetics and molecular medicine suggests that the family history is no longer limited to risk identification during obstetric prenatal counseling and ambulatory primary care, and may have direct applications in all areas of health care including the intensive care unit. For example, consider the postoperative patient with bleeding who has a positive family history of von Willebrand’s disease. Knowledge of the family history in this case would guide the diagnostic work up and direct management in a timely manner. In light of the potential value of family history information and the expanding use of genetic information, it may be time to include F for Family history in the primary survey.

A detailed family history provides the “first genetic screen” for an individual and contains substantial medical information; however, many patients are unaware of their own family histories and health care providers underutilize it. As genetic testing becomes available and more commonly used, and the medical field embraces primary prevention and early intervention, the “genetic family history” will become increasingly important in clinical decision making, especially before overt disease manifestation. Many efforts are currently being directed toward increasing awareness of the value of the family history and identifying efficient ways to implement the use of family history information.

The purpose of this review is to define the genetic family history, describe the practical use of the pedigree in interpreting the family history, and describe how genetics is leading to the reemergence of family history use. An example describing ascertainment of the family history will illustrate the value of a detailed family history. In summary, in addition to its role as an essential tool for the geneticist, family history has a central utility for all health care providers and renewed impact on clinical management in the emerging genetic era.

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The Family History

The Origins of the Family History

The origins of the medical family history ultimately trace to genealogy. Genealogy is the study of a person's identity as defined by ancestry and vital records. Typically, this includes an extended family tree defining biologic relationships and certificates documenting basic milestones in life such as birth, marriage and death. The death certificate often includes the cause of death and is essentially a piece of medical information. In addition, facts regarding education, occupation and medical health are often compiled. Taken together, this collection of information defines an individual as part of a larger biologic system, namely the family, and the family tree identifies among other things the patterns of disease present in a particular family. Therefore, genealogy defined many of the basic tenets of the medical family history.

The medical family history traces to antiquity. Hippocrates is generally credited with developing "case histories" which included observations regarding the importance of family history in addition to clinical evaluation in the role of disease manifestation [1]. His emphasis on prognosis, at a time when treatment was limited, was largely informed by the observation that disease type and severity often appeared to "run in families". This was the precursor to risk stratification. The modern medical family history is a record of illnesses and other pertinent health issues among family members [2]. Conventional, albeit underused, applications of the family history include confirming medical diagnoses, identifying family members at risk for various conditions and calculating risk for developing a particular disease [3–5].

As more is learned about the genetic basis of disease, the family history has evolved into "the first genetic screen". Since the experiments of Gregor Mendel, an Austrian priest, in the mid 1800s, our understanding of genetic information has been increasing exponentially. Mendel was interested in the theory of evolution and specifically how atypical traits developed in plants. His experiments recording the inheritance of traits in pea plants were reported in 1865; however, they were not appreciated for nearly forty years until after his death when his paper "Experiments in Plant Hybridization" was translated into English and published in the *Journal of the Royal Horticultural Society* in 1901 [6]. This study stands as the basis of our understanding of heredity and heralded the study of modern human genetics. Taken together, genetic information promises to complement and advance the value of the family history.

Obtaining the Family History

A medical family history can be *abbreviated* or *detailed* [2]. An abbreviated family history entails questioning the person of interest. This approach however is prone to misinformation and omission because it relies on the knowledge and memory of one person. Several screening tools have been developed to obtain a cursory family history, such as SCREEN (see Table 1) [7], which identifies both general family history information and areas in need of more detailed information. This approach is a useful starting point in obtaining a detailed or "complete" family history. Ascertainment of medical history can be both open-ended and focused on a specific organ system. For example, common disease categories may be reviewed initially, including coronary artery disease, diabetes, hypertension, breast/ovarian cancer, colon cancer, Mendelian conditions and reproductive risk; and subsequently the answers to these broad questions can direct the ascertainment of detailed organ-specific information.

A detailed family history refers to questioning multiple individuals within a family and requires specific demographic information (e.g., age at disease onset) and documentation of disease and other pertinent health issues by medical record review. For example, when the initial review reveals a family history significant for coronary artery disease, problem specific questions pertaining to the cardiovascular system may be pursued, including those listed in Table 2 [2,

8,9]. This approach can be applied to all relevant organ systems in obtaining a detailed family history. This is time intensive and unfortunately generally reserved for clinical genetics and research purposes; however, it is easy to appreciate the clinical value of exhaustively collected, organized and accessible family history information. The results of a detailed family history may warrant referral to a genetics service. The indications for referral are context specific and may include known genetic conditions, multiple family members with the same condition, and the presence of congenital malformations [10,11]. A detailed family history can help establish a diagnosis and initiate comprehensive care when needed.

Constructing the Pedigree

A pedigree, also known as a family tree, is a graphic representation of a family history using symbols [2,12]. The pedigree is used for many clinical and research purposes including: making a diagnosis, establishing a pattern of inheritance, identifying family members at risk, calculating risk, deciding testing and surveillance strategies, and patient education [2,13–16]. Importantly, the pedigree facilitates a patient's understanding of disease by illustrating the central observations of a medical family history and promoting conversation that clarifies misconceptions about disease and heritability. The pedigree is the primary mode of communication in both clinical genetics and human genetics research. Given the universal use of this tool, the National Society of Genetic Counselors formed a Pedigree Standardization Task Force and developed standard nomenclature for pedigrees [17]. As a result of this effort, there is a system of common symbols used to consistently communicate relationships and health status. Since the family history impacts all areas of medicine, it is important that all health care professionals have a working knowledge of pedigree structure.

A complete pedigree includes identification of the index case or proband (the person of interest) and detailed medical history as described above from at least three generations. The family is organized by generation such that each generation is on a different line and designated by sequential Roman numerals from top to bottom and each individual is given an Arabic number reading from left to right (see Figure 1, panel C). This numbering system facilitates analysis by allowing easy identification of individuals. Lines connect the symbols and establish relationships. An arrow identifies the index case. Squares designate males, circles designate females and diamonds designate unknown gender or multiple individuals. Different parts of a symbol may be filled in to represent specific medical conditions, and a legend is provided for precise reporting. In addition to illnesses, other significant health information can be recorded, including death, miscarriage and twinning. A question mark indicates that medical information for a particular person is unknown or unavailable. It is important for both clinical risk stratification and human genetics research to distinguish an individual with an unknown status from an individual who has been evaluated and is known to be "normal". Accurate and precise individual evaluation cannot be overemphasized. Since genetic information has become increasingly available, genetic data is often incorporated into the pedigree. A plus sign associated with a symbol indicates the presence of a particular genotype. A carefully constructed pedigree provides a succinct illustration of the family history and can be a powerful tool for patient education, genetic counseling and research.

The family history is dynamic; medical information within families changes over time and needs to be revisited and updated. Some affected individuals may develop different or related conditions. In addition, many "healthy", "normal" individuals may be diagnosed with disease later in life consequently changing the overall record of disease within the family significantly. Accordingly, the pedigree needs to be updated regularly. Information on unaffected individuals is equally important. Once the detailed family history is obtained, significant time needs to be invested to maintain the accuracy and value of the information [18]. As family history

awareness improves and health care providers invest more time in obtaining detailed family histories, a potential challenge will be keeping the information up-to-date and relevant.

Barriers to Using the Family History

There are significant barriers to the optimal use of family history information, primarily a lack of awareness on the family's part and considerable time restrictions on the health care professional's part. Studies have shown that a majority of people do not know their family history and do not appreciate its relevance in medical management, and consequently the potential impact of family history information is diminished [3,19–21]. Several reports have shown that patients often have poor recall regarding their own diagnoses and limited knowledge regarding illnesses present within their family. In addition, parents of pediatric patients with chronic diseases often do not know the specific diagnoses of their children [22]. In an effort to increase family history awareness, tools have been developed and are available to the general public to generate and maintain a detailed family history. For example, the Health and Human Services Family History Initiative has designed a publicly available, web-based program providing a means to generate and maintain a detailed family history [3](for this and other resources, see Table 3). Efforts to improve family history awareness and develop comprehensive family history tools are ongoing.

The time investment required for thorough review of the family history often precludes completion of a detailed family history. In the ambulatory primary care setting, Acheson et al found that family history was discussed in only one half of new patient visits and less than one quarter of return visits [20]. Further, when family history was discussed it was allotted less than three minutes time. Taken together, these findings suggest that family history is selectively performed, abbreviated in nature and suboptimally maintained [22,23]. The authors point out that time constraints in most health care settings including the clinic make it difficult to complete an abbreviated family history let alone a detailed or updated family history. In addition to significant practical limitations, many health care providers including doctors do not have formal training in genetics and are not comfortable with genetic counseling [19,24]. Nursing however has taken the lead in educating health care professionals to increase the hands-on use of genetic information [25]. One potential approach entails organizing family history information by sending patients a detailed questionnaire to be filled out prior to the encounter and providing resources at the time of the visit to develop and maintain their family history. Ultimately, efforts to prioritize family history information will require overcoming major limitations in a creative way, potentially including increased patient involvement in record maintenance and increased resource allocation by health care administration.

Family History as Patient Empowerment

Public health initiatives have recommended using the medical family history as an educational tool and developing a comprehensive record that can be kept by the patient requiring only regular updating [4,24,26]. This would accomplish both increased awareness of family history and compilation of important information that can be used in multiple medical contexts. For example, one may carry their family history and pedigree like an immunization record, so in the event of an emergency or new health concern that information is readily available. Public and professional education regarding the value of family history is needed. In addition, substantial resource allocation and organization will be needed to effectively obtain, analyze and maintain this sort of information. Ultimately, increased family history awareness leads to increased medical awareness, and with increased understanding of health and disease there is probably improved adherence and better overall care.

How does Genetics Impact the Family History?

Genotype-Phenotype

An individual's "genotype" is a person's overall genetic constitution and may refer specifically to sequence variations that can cause or increase the susceptibility of disease. Informally, a person is "genotype-positive" if they have the sequence variation in question. An individual's "phenotype" is the observable characteristics of that individual, including for example eye color, serum cholesterol levels or the presence of heart valve disease, such that the phenotype is the manifestation of the genotype. For instance, a person with Williams-Beuren syndrome (MIM#194050) has a microdeletion on chromosome 7 resulting in the loss of function of several genes (genotype), which can manifest as dysmorphism, impaired cognition and arteriopathy (phenotype). It is important to note that one genotype may result in different phenotypes and that not all phenotypes will be outwardly observable. Some phenotypic differences can only be appreciated after laboratory analysis. There is increasing interest in genotype-phenotype relationships, i.e. associations between specific genotypes and phenotypes that may be clinically informative. For example, in a patient with Williams-Beuren syndrome, loss of function of the elastin gene within the microdeletion results in arteriopathy, while cognitive impairment has been attributed to loss of function of the LIMK1 gene. The ability to stratify specific phenotypes with specific genotypes informs our understanding of the mechanisms underlying disease and has the potential to direct medical care.

Heritability

Traits or illnesses within a family are often referred to interchangeably as "familial" or "heritable"; however, heritability has a more specific meaning. Traits are familial if members of the same family share them for any reason; traits are only *heritable* if the similarity arises specifically due to shared genotypes. Heritability is the proportion of phenotypic variation due to genetic effects. Heritability of human traits including disease states is estimated using careful phenotype data and complex statistical methods [27]. A high heritability suggests that major genetic effects cause a particular trait. Therefore, a high heritability predicts that genetic discovery studies, e.g. linkage analysis and genome wide association studies should be able to identify disease loci and ultimately disease causing gene mutations.

Pedigree analysis and human genetics research of heritable diseases can be confounded by several phenomena. Confounding factors include genetic heterogeneity, variable expressivity and reduced penetrance. Genetic heterogeneity is present when different genotypes result in the same phenotype. Variable expressivity is present when the same genotype results in different phenotypes. Reduced penetrance is present when a specific genotype results in a phenotype only a proportion of the time, i.e. there are individuals who have the genotype in question but do not manifest the phenotype. These phenomena are common and have been shown to be present in varying degrees in many diseases, including pediatric heart disease [28,29].

DNA Sequence Variation

A sequence variation may be a gene mutation or a polymorphism. In general, a mutation is a variation in DNA that leads to altered gene function. There are many types of mutations including single base substitutions, insertions and deletions. Mutations can be deleterious and result in disease or they can be neutral or beneficial. Polymorphisms are common sequence variations that are generally not thought to cause pathology directly. Classic Mendelian diseases such as inborn errors of metabolism tend to be rare and caused by gene mutations, while complex diseases (those caused by a combination of genetic and environmental factors) such as coronary artery disease or type 2 diabetes tend to be common and associated with polymorphisms. For example, single nucleotide polymorphisms (SNPs) have been associated

with an increased susceptibility or predisposition to disease. While family history has been established as an independent risk factor for many common complex diseases, including coronary artery disease, hyperlipidemia and type 2 diabetes [4,13,14,23,30,31], there is an increasing appreciation that polymorphisms may also identify disease susceptibility complementing the family history. Identification of a genotype in the presence or absence of a positive family history prior to the manifestation of disease may have significant implications. For example, screening strategies, treatment and counseling may all be modified as a result of genotype knowledge. It remains unclear whether or to what extent the identification of sequence variations will provide an incremental benefit in risk stratification over family history information or will identify clinically relevant genotype-phenotype relationships.

Genetic Screening for Breast Cancer: an Example

Screening for mutations or polymorphisms that are associated with disease risk is now possible and can be performed in those considered at increased risk by family history. Since these markers can be identified prior to the development of disease, they may potentially lead to medical intervention prior to disease onset to delay or abrogate the manifestation of disease. Recently, a family was reported that illustrated the potential actions that can be taken by an individual who carries a gene mutation associated with disease but does not presently manifest any evidence of disease [32]. A 33 year-old woman with a strong family history of breast and ovarian cancer decided to undergo screening and learned she carried a mutation in the BRCA1 gene. She was confronted with difficult and controversial options including increased medical surveillance and preemptive removal of her breasts and ovaries. She decided to proceed with prophylactic mastectomy deferring removal of her ovaries until after she has had children. The ability to make a diagnosis based on genetics prior to the onset of disease has the potential to shift the paradigm of medical treatment to primary prevention and early intervention.

Genetic Screening for Sudden Cardiac Death: an Example

Hypertrophic cardiomyopathy and long QT syndrome are common causes of sudden death in the young. Hypertrophic cardiomyopathy, characterized by hypertrophy, myocyte disarray and interstitial fibrosis, has been associated with mutations in sarcomeric genes. Patients with hypertrophic cardiomyopathy and a mutation in the troponin T gene are at increased risk for sudden cardiac death despite a relatively mild degree of hypertrophy. In addition, patients with specific mutations in the beta myosin heavy chain gene are also at greater risk for sudden cardiac death. These genotype phenotype relationships impact clinical screening strategies and genetic counseling. Long QT syndrome, characterized by prolonged ventricular repolarization and ventricular tachycardia, has been associated with multiple genes, the vast majority of cases due to mutations in one of three ion channel genes. Patients with long QT syndrome and mutations in either the KCNH2 or SCN5A genes appear to be at increased risk for cardiac events, impacting counseling and potentially decision making regarding the placement of an implantable cardioverter defibrillator. As medicine increasingly moves from diagnosis and treatment to screening and prevention, the family history will play an expanding role in clinical decision making. For example, all first-degree relatives of index cases with hypertrophic cardiomyopathy or long QT syndrome may obtain genetic testing and if positive then undergo more aggressive clinical surveillance or intervention in an effort to prevent sudden cardiac death prior to any sign of disease. Many genetic diagnoses require comprehensive care and outcomes are improved by early coordination of care and early intervention. This approach shifts the emphasis from treating end stage disease to treating anticipated disease.

Genetic Screening for Pediatric Heart Disease: an Example

Family history also has a central role in the understanding of pediatric heart disease. Pediatric heart disease can be defined as cardiovascular disease in the young including cardiovascular

malformations (CVMs, also known as congenital heart defects), arrhythmias, cardiomyopathies and vasculopathies. Pediatric heart disease is present in approximately 7 per 100 live births, and if one considers fetal abnormalities that result in spontaneous abortion prior to live birth, the incidence of CVM is at least five times higher [33,34]. While an association between CVM and genetic syndromes has been established, the appreciation of single gene defects as a cause of nonsyndromic CVM has increased substantially in recent years. Over 1000 gene tests are now clinically available including many for CVM in the context of a genetic syndrome; however, genetic testing for nonsyndromic CVM is primarily available on a research basis at this time (see <http://www.genetests.org>) [35,36].

Using the Genetic Family History in Research

The Working Genetics Research Paradigm

Historically, genetic information was primarily ascertained from monogenic disorders that have unambiguous phenotypes and follow classic Mendelian inheritance and account for approximately 5% of all disease; however, genetic information is rapidly being applied in novel ways to enhance diagnosis, risk stratification and treatment in common complex diseases. The family history remains at the center of these efforts. Human genetic studies depend on precise and accurate phenotyping. Investigators appreciate that anything less, particularly in control groups, imposes major limitations in data analysis [37]. Despite thoroughly evaluating presumably normal participants, there are some factors that cannot be controlled. For example, at the time of evaluation, there is no way to know whether the individual is “normal” or simply has not manifested disease yet. In so far as it is possible, strict and narrow phenotype criteria facilitate accurate individual classification. Careful phenotyping is paramount once genetic cause is established and genotype-phenotype relationships can be elucidated.

The current paradigm in human genetics research involves genetic discovery (the identification of sequence variation associated with disease) followed by mechanistic investigation of the sequence variation in genetically modified animal models. Findings from human genetic studies are being taken into the laboratory where increasingly sophisticated animal models are providing the basis to define pathogenesis in a variety of diseases. The elucidation of pathogenesis in turn results in the development of new diagnostic and therapeutic strategies which can then be taken back to the patient. Taken together, this is referred to as the “bedside to bench to bedside” approach to disease and has led to numerous initiatives aiming to realize “translational” research goals. The Human Genome Project has reported the entire human sequence [38,39], and this achievement will facilitate the search for disease causing genes and important sequence variation involved in the pathogenesis of complex diseases. Genetic information is also impacting the understanding of pharmacology as it relates to drug indications and drug responses further facilitating improved care. Taken together, genetic information provides an impetus to shift the focus of medicine from treatment of end stage disease to strategies emphasizing primary prevention and early intervention.

Hypoplastic Left Heart Syndrome: an Example

To illustrate how a detailed family history may be obtained and completed, the methods of an ongoing family-based study will be described. A human genetics study is currently enrolling families identified by an index case with hypoplastic left heart syndrome (HLHS) to identify the genetic causes of HLHS and associated CVM. HLHS (MIM#241550) is a severe CVM that continues to be a significant cause of infant mortality and childhood morbidity. Left sided congenital CVMs, such as bicuspid aortic valve (BAV, MIM109730), aortic coarctation and HLHS are thought to be causally related based on epidemiology studies that found familial clustering of these lesions. To date, over 50 families have been recruited and nearly 250 family members have been evaluated. More than half of these families have at least one individual

with CVM in addition to the index case, demonstrating that these families are enriched for CVM. When a family is recruited, a detailed family history (minimum three-generation) is obtained. A sequential sampling strategy is employed, i.e. each index case's first-degree relatives are evaluated and for every new affected individual identified, all of that person's first-degree relatives are evaluated. When the family history identifies a second-degree relative that is affected, all of that person's first-degree relatives are evaluated. Each family member that is evaluated undergoes phlebotomy for DNA analysis and an echocardiogram for evaluation of cardiac anatomy. All family members undergo echocardiographic screening even if they are otherwise "healthy". Careful phenotyping is critical since BAV often is subclinical.

Family history was reviewed with at least two family members on at least three separate occasions. In 28/38 (74%) kindreds, the initial family history was not altered by subsequent inquiries. However, in 10/38 (26%) families, information relevant to the study was either revised or discovered upon subsequent queries and in all instances led to the discovery of a multiplex kindred. In 4/10 (40%) of these families, significant revisions on multiple occasions were necessary to arrive at a "complete" family history.

For example, the family represented in Figure 1 shows the development of family history information. The index case (individual IV-1, indicated by an arrowhead) was diagnosed at birth and transferred to a cardiac intensive care unit for further care. Upon admission, the family history was taken from the father and noted to be "noncontributory". During the course of the hospitalization, the family was approached to invite participation in the human genetics study. At that time a detailed family history was obtained from the mother and it was discovered that the maternal great grandmother (I-2) had a history of BAV and aortic valve disease requiring aortic valve replacement underscoring the importance of talking with different people within the same family to gather all relevant information. Medical records including imaging reports and operative reports were obtained to confirm the family history and document specific medical details. Subsequently, two previously unknown cases of BAV were identified by screening echocardiography in the father (III-1) and a sibling (IV-2). The discovery of subclinical CVM highlights the importance of careful phenotyping and screening first-degree relatives at risk (Individuals with BAV are at increased risk for developing aortic valve disease, infective endocarditis and aortic root dissection). The mother (III-2) and maternal grandfather (II-3) are obligate carriers and therefore presumably have the genotype associated with disease without any evidence of the phenotype. Taken together, pedigree analysis of this family is consistent with autosomal recessive inheritance and reduced penetrance.

HLHS and associated CVM has a heritability of 74%, suggesting that HLHS is caused largely by genetic factors [40]. This high heritability predicts that areas of the genome can be mapped and disease-causing genes identified. This in turn may lead to the development of genetically modified animal models of HLHS and an improved understanding of pathogenesis. Ultimately, this may lead to new strategies directed at diagnosis and treatment. A better understanding of the genetic basis of HLHS may refine the way we think about CVM. The current taxonomy of CVM is based on anatomy, and it is unclear how genetic insight may improve our understanding of the clinical taxonomy.

The frequency of first-degree relatives with HLHS or CVM is approximately 3% and 18%. Siblings of HLHS index cases were diagnosed with HLHS in 8% of cases and any CVM in 22% of cases. Recurrence risk ratios for both first-degree relatives and siblings were significantly increased. If one parent was affected with CVM, the frequency and recurrence risk ratios of siblings with either HLHS or CVM increased substantially [40]. This suggests that epidemiology based recurrence risk calculations underestimate risk, possibly due to incomplete phenotyping of first degree relatives, and this should be taken into consideration when counseling families.

A strength of this approach is the use of a strict phenotype definition of HLHS and precise echocardiographic phenotyping. Human genetic studies depend on careful and accurate phenotyping. Left ventricular hypoplasia, a feature of several different CVMs (e.g. unbalanced atrioventricular septal defect) believed to have diverse developmental origins, is often referred to as HLHS based in part on the similarity of the surgical treatment strategy of individuals with a left ventricular hypoplasia. This results in the generic use of “HLHS” in the literature, which is problematic when considering the genetic basis of HLHS. Combining echocardiography, which obtains detailed and definitive phenotype information, with a narrow well-defined index case definition provides consistent and specific results. Our findings also demonstrate the benefit of a thorough detailed family history in human genetics research, and emphasize both the need to revisit the family history vigilantly and the medical value of family history awareness.

Summary

Genetics has transformed the use of family history information and has led to the reemergence of the detailed genetic family history (see Table 4). It is critical that public and professional educational efforts to increase family history awareness and working knowledge are prioritized. Patient maintenance of the pedigree will provide increased patient awareness and facilitate some of the limitations associated with conventional medical history ascertainment and ultimately will improve health care. Detailed family history information is superior to abbreviated family history information, and detailed family histories will be necessary for the optimal use of genetic screening. Finally, the increasing use of genetic screening promises to cultivate a paradigm shift in medical treatment emphasizing primary prevention and early intervention. Appreciation of the family history will be necessary to make this important advance.

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Figure 1.

The development of a detailed “complete” family history. After a new diagnosis of HLHS was established in an infant (IV-1, arrowhead), an abbreviated family history was noted to be “noncontributory” (panel A). Upon ascertainment of a detailed family history obtained from multiple family members (panel B), the family history was noted to be significant for BAV requiring AVR in a maternal great-grandmother (I-2). Finally, upon screening echocardiography, two cases of subclinical BAV were discovered (III-1 and IV-2, panel C) revealing a family enriched for cardiovascular malformation. Individuals II-3 and III-2 are obligate carriers (dots). Pedigree analysis is consistent with autosomal recessive inheritance with reduced penetrance. AVR aortic valve replacement; BAV bicuspid aortic valve; HLHS hypoplastic left heart syndrome.

Table 1

Abbreviated Family History: SCREEN for Familial Disease.

SC	Some Concern	Do you have any concern about diseases that run in the family?
R	Reproduction	Have there been complicated pregnancies, infertility or birth defects?
E	Early disease/death	Has anyone in your family become sick or died at an early age?
E	Ethnicity	How would you describe your ethnicity?
N	Non-genetic	Are there risk factors that run in your family?

Table 2**Detailed Family History: Questions for Cardiac Disease***Information on family members*

Is there a history of coronary artery disease, cardiomyopathy, arrhythmia or congenital heart disease?
 Is there a history of sudden death or childhood death? What age? (obtain reports)
 Is there a history of pregnancy loss?
 Is there a history of consanguinity?
 Does anyone have a pacemaker?
 Does anyone need to take antibiotics prior to medical/dental procedures?
 Does anyone have facial dysmorphism? (genetic syndromes often associated with cardiac malformation)
 Is there a history of neuromuscular disease? (Duchenne Muscular Dystrophy, Friedreich's ataxia)
 Is there a history of hearing loss? (LQTS)
 Is there a history of unusual skin findings? (Dyslipoproteinemias and Connective Tissue Disorders)
 Is there a history of unusually short or tall stature? (Marfan, Turner and Noonan syndromes)
 Is there a history of loose joints? (Marfan and Ehlers-Danlos syndromes)

Information on affected individuals

At what age was heart disease diagnosed?
 Is the person living or deceased? (if deceased, obtain autopsy report)
 Does this person have other medical problems?
 Has surgery been performed? (obtain operative and pathology reports)
 Have diagnostic studies been performed? (obtain reports)
 What medications does the person take?
 Is there a history of alcohol or tobacco use? How much?

Table 3**Resources for Genetic Family History Ascertainment and Awareness**

Health and Human Services Family History Initiative	www.hhs.gov/familyhistory
Online Mendelian Inheritance of Man	www.ncbi.nlm.nih.gov/Omim
Centers for Disease Control	www.cdc.gov/genomics
March of Dimes	www.marchofdimes.com
National Coalition for Health Professional Education in Genetics	www.nchpeg.org
American Medical Association	www.ama-assn.org

Table 4**Summary: Take Home Messages**

A detailed family history is necessary for optimal clinical use and research
The family history must be obtained from multiple family members on different occasions
The “complete” family history must be revisited regularly
The pedigree is a useful tool for consolidating medical information and patient education
There are informative and useful web-based resources for patients and health care providers
The family history is critical to the continued success of human genetics research
The family history may indicate genetic screening which in turn may direct medical care