

The Genetic Family History

in practice

Is a Universal Family History Tool Feasible?

by Robin Bennett, MS, CGC

Perspectives from the NCHPEG Family History Working Group

In 1974 Microsoft founder Bill Gates stated, "We started with a vision of a computer on every desk and in every home." His vision is close to reality just 30 years later. Perhaps NCHPEG's mantra should be, "A pedigree in every patient's chart." In fact, NCHPEG's Core Competencies in Genetics recommend that all health providers understand the importance of family history (three generations) in assessing predisposition to disease, that all health providers be able to compile a multigenerational genetic family history, and that all providers appreciate the need for privacy and confidentiality when dealing with genetic information. Wouldn't the best way to assure these competencies be to develop a family history tool for use by every practitioner and for placement in every patient's medical record?

During the last three years the NCHPEG family history working group contemplated creating such a tool, but faced a myriad of challenges. Could one family history tool meet all needs? The family history information obtained for pediatric, prenatal, adult, oncology, or emergency room visits is quite different. How extensive does the information collected need to be? What is the ideal format for a universal family history tool: a questionnaire, a hand-drawn pedigree based on a survey, an online form, a touch-screen computer kiosk in the health professional's office? Who should use the tool: the patient, the receptionist, the health care provider? When should the information be collected: at the visit, or before the visit?

Of primary importance, what is the purpose of completing a universal family history tool? Is the purpose to collect enough information to perform genetic risk assessment, or is it to highlight patterns suggestive of genetic risk so that a provider can refer to a genetics specialist?

How would the users of the tool ensure that the information collected was accurate (e.g., is it necessary to obtain medical records for validation)? Can a universal tool transcend cultural differences in describing disease and patients' willingness to discuss private information? Could it be translated effectively into multiple languages at an elementary reading level? How would a universal family history tool best be incorporated into practice as health professionals shift to electronic medical records? And, how easily could such a tool be updated to reflect changes in disease status and the deaths and births of relatives?

The working group unanimously agreed on three things: 1) there cannot be a universal family history tool because different patient populations and clinical specialties have different needs, 2) any proposed tool would need to be validated, and 3) creating a tool that has undergone appropriate validation costs money. So, instead of attempting to create and validate a universal family history tool, the group decided to create a template to describe and evaluate pedigree tools that are already available. Some of the review questions proposed by the working group include:

- Is the form appropriate for the patient population and demographics?
- What is the format (e.g., paper, Web based, PDA)?
- Over what time period has the tool been used?
- Who fills out the form and in what setting (e.g., patient or office personnel; at home or office kiosk)?
- What is the extent of the information collected about relatives? Is this enough information to generate a pedigree?

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Proceed with caution:

We may have 20/20 hindsight, but we are still blind to the biases of our own time.

by Robin Bennett, MS, CGC

The past reminds us that we must proceed cautiously as we develop instruments that gather personal and family health information. At the turn of the last century, the Eugenics Record Office (ERO) in Cold Spring Harbor, N.Y., encouraged citizens to record standard family histories of what the ERO called "objective traits," which included "insanity," "neuroses," "epilepsy," "feeble-mindedness," "mental defectiveness," "pauperism," and "wanderlust" (see page 2). These American "blood lines" were collected for the purpose of "...accumulating and studying records of physical and mental characteristics of human families to the end that the people may be better advised as to fit and unfit marriages," and to "establish the potentialities of an individual" (Mazumdar, 1992).

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Proceed with caution:

Continued from page 1

With the clarity of hindsight, modern health professionals shudder at the biases of these early pedigrees and the atrocities that many eugenics policies produced. But, what "bad" traits are we now attempting to screen for as we develop family history tools, and for what purpose? As genetic counselor Robert Resta (1995) notes, "...in genetics as in all scientific pursuits, the construction and interpretation of a pedigree can be influenced by the political and social beliefs of all-too-human geneticists. Those beliefs may be so ingrained that we mistake them for biological laws. It is, I suspect, beyond our ability to know which of our personal biases we are disguising as scientific truths. The whispers and hints of our biases may be heard only by future generations of geneticists."

References:

- Bennett RL, Pedigree Parables. Clinical Genetics 2000; 58:241-249.
- Mazumdar PMH. Eugenics, Human Genetics and Human Failings. London: Routledge, 1992.
- Resta RG. Whispered hints. Am J Med Genet 1995;59:131-133

- Is the form or a subsequent pedigree placed in the patient record?
- Is the family history tool available in other languages, and has it been used in populations with varying ethnic and socioeconomic status?
- How long does it take to complete?
- Is risk-assessment information provided, and if so, is this information available to the patient or to the health professional? What is the format of the assessment (e.g., risk stratification such as high or low, or an actual percentage)?

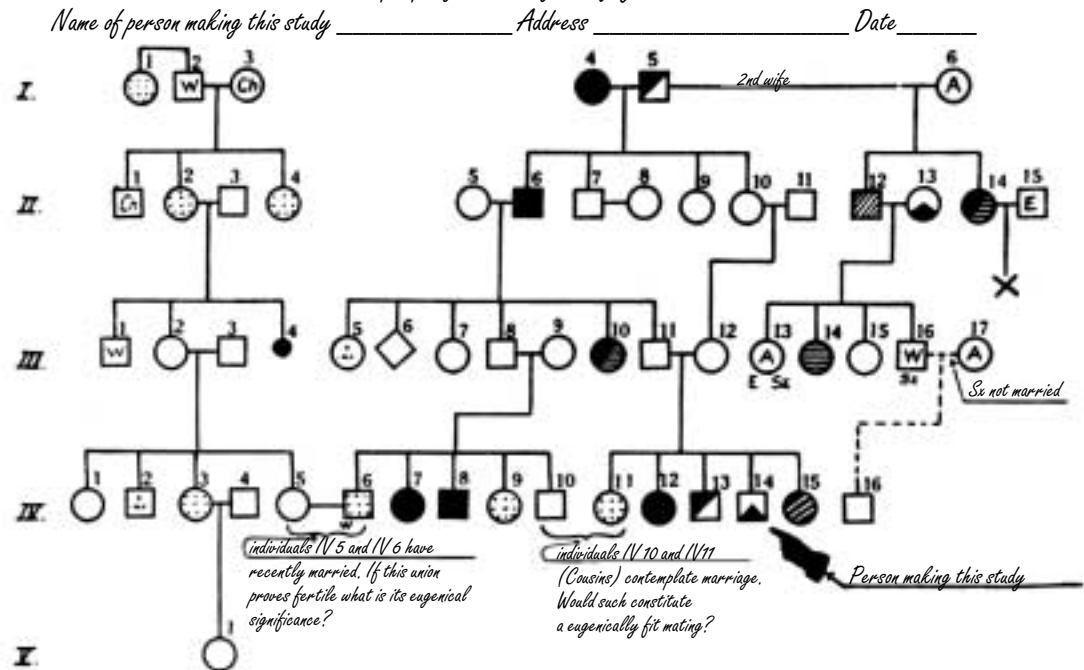
- Has the tool been validated, and if so, how?

NCHPEG's family history working group will continue to feature family history tools and resources for use in teaching and clinical practice in this newsletter, and hopes that the review template will help providers find the most appropriate tool for their patient populations. The full version of the family history review template is available on the NCHPEG website at www.nchpeg.org.

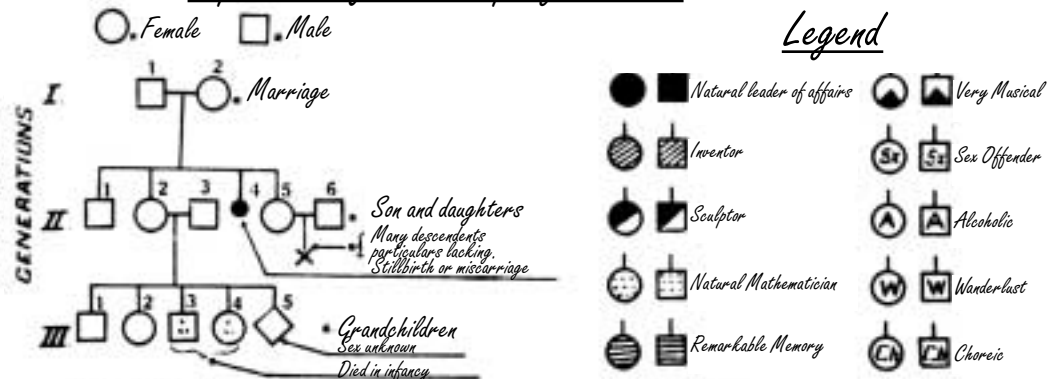
Brief instructions for constructing a Pedigree Chart

and for designating the family distribution of specific traits preparatory to making a descriptive analysis of the innate traits of each individual.

Small sample pedigree showing use of symbols, etc.



Explanation of the above pedigree



An explanation similar to this one should accompany each chart. The letters or symbols representing the traits characteristic of the family studied are arbitrarily chosen by the person making the chart. Only a few symbols and those for defects have been standardized—eg— I-insane, F-feeble-minded, Ch-choreic, E-epileptic, A-alcoholic, etc., etc. Note: Such a chart is only the beginning of a eugenical study but it is very useful for showing graphically the family tree and for indicating in a general way the most striking traits of its various members. In order to determine the hereditary potentialities of an individual, each of the several members of his or her family network must be described—both good qualities and defects—with care, accuracy and frankness. For this purpose, the individual analysis card is supplied.

The Case of Laura

HEREDITARY COLON CANCER

Given a striking history of colon cancer, early detection becomes a family affair

R.T. Bassett, MS, CGC

The case of Laura, a 30-year-old woman with a family history of colon cancer, exemplifies the benefit of taking the time to elicit a family history. In this situation, a three-generation family history had a positive effect on the health of an entire family.

Laura presented to her primary care physician for a physical exam required by her new employer. Laura's 57-year-old mother had colon cancer at 42 years of age and underwent a total colectomy upon the discovery of thousands of polyps in her colon. Laura had never had a colonoscopy, despite a significant family history of colon polyps and colorectal cancer. Of her 13 brothers and sisters, one brother was diagnosed with colon cancer at 37 years of age, a sister had multiple adenomatous colon polyps removed at 41, and another sister, 34, recently had multiple colon polyps identified by colonoscopy. Furthermore, Laura's maternal aunt, who died of accidental causes in her twenties, had been diagnosed in childhood with a hepatoblastoma (a malignant liver tumor associated with familial colon cancer), and her maternal uncle died at 57 of colon cancer.

Laura's primary care physician referred her to a genetic counselor to discuss her family history, screening recommendations, and genetic testing. Laura's counselor described hereditary colon cancer syndromes, and informed Laura that her family history was consistent with a condition known as familial adenomatous polyposis (FAP).

FAP is a colon-cancer syndrome in which hundreds to thousands of precancerous colonic polyps develop beginning at a mean age of 16 years. By 35 years of age, 95 percent of individuals with FAP have colon polyps, and

without colectomy, colon cancer is inevitable. The mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP is inherited in an autosomal dominant manner, which confers a 50 percent risk that the siblings and offspring of an affected individual may also be affected.

Laura decided to discuss genetic testing with other members of her family. As explained by the genetic counselor, it would be advantageous to offer genetic testing to Laura's mother first, as she was known to be affected with colon cancer. If her mother did not carry the associated genetic variation, the probability of FAP within her family would be extremely low. Laura's mother agreed to undergo genetic testing, and the test results revealed a mutation in her APC gene, which causes FAP. As a result, Laura and her siblings had a 50-50 chance of having inherited the same mutation.

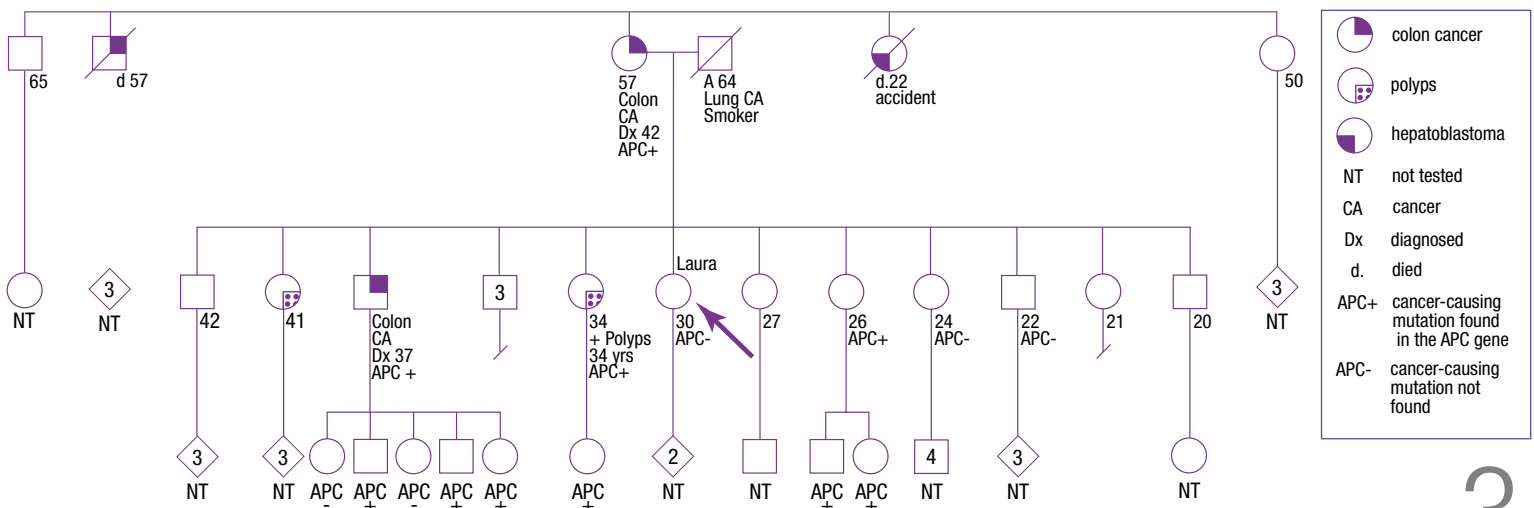
Given the recommended screening procedures and many surgical options available to patients with FAP, Laura consented to genetic testing. A negative result would mean that Laura could undergo routine population screening. A positive result, however, would mean enhanced screening (e.g., annual colonoscopy and endoscopy procedures) and consideration of surgical options.

Laura's genetic test revealed that she did not inherit the genetic mutation found in her mother, and thus she does not have FAP and her children are not at risk. The test results, however, also have implications for the extended family. Since her genetic test, five of Laura's siblings have also been tested; three of them have the APC mutation and have been diagnosed with FAP. Additionally, six of her 22

Colon cancer is the third most common cancer in the United States, with about 150,000 cases occurring each year. There are hereditary and non-hereditary forms of colorectal cancer. In about five percent of colon cancer cases, a predisposition is inherited through generations in the family. The four most common colon cancer syndromes are hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), Muir-Torre syndrome, and Turcot syndrome. For families affected by these cancers, education and genetic testing may result in earlier and more frequent screening as well as surgical options. Furthermore, genetic testing of at-risk individuals will help guide the healthcare team in disease management, treatment, and counseling. Family history often is the key to early detection in familial colon cancer cases, and early detection is the key to survival.

nieces and nephews, all under the age of 17, have tested positive for the familial APC mutation that causes FAP and have initiated screening by colonoscopy and endoscopy.

A family history taken by a primary care physician may signal the need for referrals to appropriate specialists, including in this case a genetic counselor, gastroenterologist, and psychologist. Furthermore, this case illustrates the far-reaching ramifications of a detailed family history in the context of primary care practice and emphasizes the vital role a primary provider can play in recognizing genetic risk within families.



fragile X revealed

When a Picture Is Worth 1,000 Words

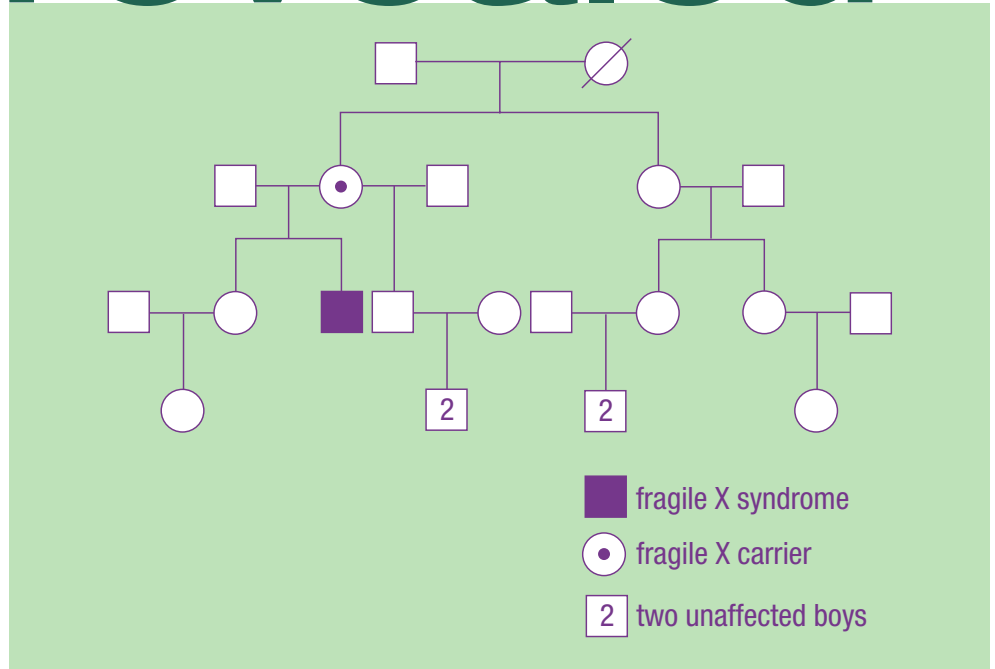
Martha Weisz Volner, MSW

Imagine my shock when, during a genetics course I took in social work school, we were shown pictures of commonly occurring syndromes, and I saw a child who looked exactly like my cousin Joe. The cousin in question and the boy in the slide both had fragile X syndrome, a frequent cause of mental retardation. Its name comes from the fact that it is inherited from a defect in the X chromosome.

My cousin, by this time in his 40s, had always had mental retardation. As a child, before the age of modern genetic medicine, he had been dragged from doctor to doctor in search of a specific diagnosis. "Impossible," said my mother, when I called to tell her of my revelation about her sister's son. "We all know he inherited the 'bad gene' from his father." (If, in fact, Joe did have fragile X, that would mean he inherited it from his mother.)

"Well, if you'd seen the picture, you'd think [Joe has fragile X] too," I said. Still doubtful, my mother asked whether she ought to tell her sister. "Do you think it would upset her? Perhaps we should let sleeping dogs lie." We battled the thought around and finally decided to tell her about our suspicions. A suspicion of fragile X in the family had implications for several other family members. I knew that it was possible for Joe's sister and her only child, a daughter, to be carriers. I knew that I, too, could be a carrier, but this chance was reduced because I already had two unaffected sons. There were several other relatives, including my sister, who were contemplating having children. What should we do with information of potentially great importance to a number of people? Did we owe it to them to share it, or would it be better not to upset them? At that time, facilities that conducted testing for fragile X were hard to find, and the test itself was not very reliable.

As it turned out, the primary emotions my cousin and my aunt felt were relief at a possible explanation for Joe's condition, and curiosity. My cousin and



aunt went immediately to the library and agreed with my assessment that the descriptions and the pictures in the references they found were a perfect match with Joe. Nonetheless, we were all dubious because of the long-standing belief that the problem came from Joe's father, a man with a long history of emotional disorders. Even Joe's father's family believed Joe's condition had been inherited from their side of the family and were astounded by the new development. Still, we had yet to confirm the diagnosis through genetic testing.

As luck would have it, I went to a conference where I met one of the principal fragile X researchers. After I told him my tale, he made me a bet that I must be mistaken in my diagnosis and agreed to test Joe's blood if I would send it to him. I did, and sure enough, I won the bet.

At that point, my sister became pregnant and, to be safe, both my mother and she were tested; neither is a carrier, but my aunt, Joe's mother, is an obligate carrier of the mutation. My mother made every effort to explain the situation to the various other relatives who also were possible carriers of fragile X. Few of them took her seriously, but we don't know whether that was because of denial or a lack of interest. To date, no other case of fragile X has emerged in my family, nor do we know of any other case in previous generations.

In terms of family dynamics, the diag-

nosis of a heritable, traceable, and testable trait turns out to be a matter not only for the individual or the nuclear family. Rather, it may well involve a considerable number of people who may have very different attitudes. The difficulty is that some may welcome the decision to share information while others may reject it or respond with anger or indifference. Before plunging in with what may be a very loaded piece of news, one should consider carefully the range of possible reactions. Further, it is difficult to tell some people and not others. Secrets of this nature may hang very heavy amongst relatives. Thus there is no one correct way to handle such a situation.

Because this was a personal and professional issue for me, it was difficult to see the options clearly. With the 20/20 vision that hindsight and great strides in this field now offer, it seems to me that health professionals such as social workers should arm themselves with information about the disorder and its pattern of inheritance, as well as the name of an appropriate support organization. (For more information about fragile X, visit www.fraxa.org.) Health professionals also should be ready with the names of knowledgeable genetic counselors or social workers who can talk to families and address their questions and concerns.

The Pedigree

by Suellen Hopfer, MS, CGC,
and Elizabeth Varga, MS

Before the Pill

Venous Thromboembolism (VTE)

VTE is a term that describes deep-vein thrombosis (DVT) or pulmonary embolism (PE). A DVT occurs when a blood clot forms in one of the large veins, usually in the lower limbs, partially or completely blocking circulation. When a fragment of the blood clot breaks loose and travels to the lung (PE), this is a life-threatening complication. Each year, an estimated 200,000 to 600,000 Americans will suffer from VTE, which may be responsible for 60,000 to 200,000 deaths annually.

Many studies have demonstrated that women using oral contraceptives (OCs) have an increased risk of venous thromboembolism (VTE), particularly in the presence of a family history of VTE. Providers of oral contraceptives are well positioned to screen younger women (ages 15-49) who may have an increased risk to develop VTE with OC use. At this time, population screening (including genetic testing for VTE risk factors) is not recommended, primarily because costs may not justify potential benefits. Using the family history as a screening tool, however, can help providers identify at-risk patients, for whom further screening and genetic testing may be appropriate.

Making the case for family history screening

Although there is no magic bullet to prevent VTE, eliciting a targeted personal and family medical history prior to prescribing OCs is a sound preventive measure. A previous thrombosis is known to be a strong risk factor. A strong family history (defined by having at least one first-degree relative who has had a VTE before age 50) also is known to be an independent risk factor. Age at first VTE is also about 10 years earlier in persons who have a positive family history for factor V Leiden mutations. Therefore, eliciting family history helps to assess the likelihood that a woman will develop thrombosis if she uses oral contraceptives. Contrary to the prevailing wisdom, being young is not necessarily protective against adverse consequences such as clotting and stroke due to OC use.

Eliciting a targeted family history prior to prescribing OCs also may raise awareness about VTE in at-risk individuals. Raising awareness can empower patients to take preventive measures in

high-risk situations such as long flights (e.g., by keeping hydrated, avoiding alcohol, wearing compression stockings, and by walking or stretching). At-risk patients may consult with their doctor before surgeries, consider alternative birth control options, or enroll in smoking cessation classes, among other strategies. Once a high-risk patient is identified through the family history, providers should counsel her about the signs and symptoms of VTE - or refer to appropriate specialists (i.e., hematologists, genetic counselors) - so that if a blood clot does occur, early diagnosis and treatment can be initiated.

Analysis of personal and family history should be standard of care prior to prescribing hormones. Women who have a predisposition for VTE should avoid third-generation OCs, because they impart a 2-3-fold increased risk of VTE over that seen in users of second-generation combination pills. Women who have a documented history of unexplained VTE, VTE associated with pregnancy or exogenous estrogen should not use combination OCs unless they are currently taking anticoagulants. Hormone replacement therapy, emergency contraception (often provided at university student health centers), estrogen, and selective estrogen-receptor modulator medications (e.g., tamoxifen and raloxifene) also should be avoided. Barrier methods (condoms, diaphragms), progestin-releasing IUDs, progestin-only OCs (minipill), or depot medroxyprogesterone acetate do not increase the risk for VTE and may be offered as alternatives for birth control.

Disadvantages of family history screening include reduced sensitivity when family size is small. Second, family history may be silent in cases with incomplete penetrance¹ and given the multifactorial nature of VTE. The predictive value of family history with respect to VTE in the U.S. is unknown, although choosing not to screen for VTE in

the family history is a missed opportunity.

Directed family medical history questions

To be an effective screening tool, the family history should include first- and second-degree family members who have had any prior clotting events (VTE), documenting their age at onset (VTE before the age of 50 should raise a red flag), the severity of the event(s), and the site of clotting episodes. Other causes for concern include recurrent second- or third-trimester fetal loss, stillbirths, maternal pregnancy complications (particularly intra or postpartum VTE -- the use of outdated terminology for DVT such as "milk leg" may assist with patient recall), known carrier status for inherited thrombophilias (e.g., factor V Leiden, prothrombin), or acquired risk factors (lupus anticoagulant or anticardiolipin antibodies).

The complexities of risk assessment for thrombosis

Primary care providers have an important role in communicating in clear, straightforward language the benefits and risks associated with OC in patients with a family history of VTE. One does not want to create panic in an OC user, who may abruptly stop taking her oral contraceptive resulting in an unintended pregnancy. Pregnancy, an acquired hypercoagulable state, confers a higher risk for VTE than does being on any combination OC. On the other hand, women who are at increased risk for VTE may still choose to use an estrogen product (e.g., combination OC) despite being counseled about increased relative risks. The goal of screening OC candidates is to identify those women for whom the VTE risk outweighs the OC benefits. For a list of references, you can contact Suellen Hopfer at sxh343@psu.edu, or Liz Varga at lvarga@kumc.edu.

¹Incomplete penetrance means that not everyone who inherits the particular genotype expresses the disease characteristics.

The Genetic Family History

This newsletter is made possible by members of the Family History Working Group, contributors, the NCHPEG staff, and funding from the National Human Genome Research Institute, the Office of Rare Diseases, and the Health Resources and Services Administration. The purpose of this thrice-yearly, online publication is to help educators and providers learn about the role of the genetic family history in health care, and to facilitate access to family history resources for use in teaching and clinical practice.

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Please send your comments, questions, or any materials you would like to submit for the next newsletter to Erin K. Herrick, NCHPEG Project Director (e-mail ekherrick@nchpeg.org, phone: 410-583-0600, fax: 410-583-0520), or to Robin Bennett, Chair of the NCHPEG Family History Working Group (robinb@u.washington.edu).



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On the web

Your Family History – Your Future

Barbara Pettersen, MS, CGC

A family medical history tool designed for the public is now available on-line. The National Society of Genetic Counselors, Genetic Alliance, and the American Society of Human Genetics collaborated to create a tool to empower individuals to collect family medical history information and draw their own pedigrees. Health professionals may have little time to collect extensive family history information, but health-care consumers can be encouraged to bring their own medical pedigree to appointments. This information can help identify individuals at increased risk to develop specific medical conditions.

The hope is that raising awareness of significant health risks revealed in the family history will lead to healthy lifestyle changes for at-risk relatives. In addition, the tool emphasizes that by sharing family health histories with health care providers, people can receive more appropriate medical screening and management.

The tool was launched during the 2003 holiday season with a nationwide publicity campaign to encourage people to collect family medical history during family gatherings. A press release distributed to national media outlets included "key messages," examples of which are listed below:

- An accurate family tree is a gift of medical knowledge to future generations.
- A medical family tree will help your family identify potential health concerns and risks.
- Knowledge is power. Having your medical family history allows you to take control of your health and learn about your options, such as early detection or preventive steps.
- Medical family trees are becoming standard medical tools and can assist health care providers and genetic counselors in identifying health risks early on.
- Learning about your family history can benefit both you and your relatives...and it can be fun, too.
- Vacation, holidays, and family reunions are great times to collect the information for your medical family tree.

The family medical history tool is available on the websites of each of the collaborating organizations:

National Society of Genetic Counselors
<http://www.nsgc.org>

American Society of Human Genetics
<http://genetics.faseb.org/genetics/ashg/ashgmenu.htm>

Genetic Alliance
<http://www.geneticalliance.org>