GENETICS: THE MEDICAL FAMILY HISTORY

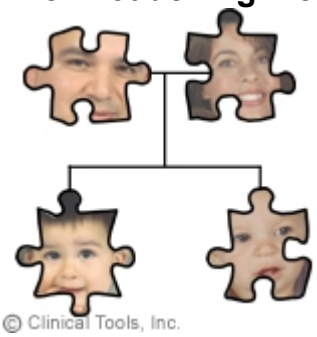
Goal:
Identify families that may benefit from genetic services using the personal and family medical history interview process.

After completing this activity participants will be able to:
- Recognize the importance of eliciting at least a 3-generation family history in primary care
- Use standard pedigree symbols and nomenclature to document a medical family history
- Recognize red flags in the medical family history
- Assess the pedigree for clues about inheritance patterns
- Utilize the pedigree to perform basic risk calculations

Professional Practice Gaps
In an effort to define what healthcare providers need to know about medical genetics, several organizations developed core competencies (NCHPEG, 2000; ASHG, 2001). However, because clinical genetics is a relatively young and evolving field of medicine, many practitioners received insufficient formal genetics education. As a result, they express a lack of confidence in their clinical genetics knowledge and a lack of confidence in their ability to provide genetic counseling.

THE IMPORTANCE OF FAMILY HISTORY

The Broadening Field of Medical Genetics



Medical genetics is no longer a narrowly defined field of medicine characterized by the study of rare conditions. Instead, we can now appreciate that most common diseases result from complex interactions between an individual's genetic makeup and his or her environment. While there is still much to be learned about these interactions, there are already opportunities to make targeted surveillance and management recommendations based on a recognized familial risk for many common conditions, including diabetes, cardiovascular disease, iron overload, venous thrombosis, and multiple different malignancies. Healthcare providers must learn to consider if there is a genetic component to whatever illness their patients may present with and then respond accordingly.

Using the Family History as a Tool

The family history has long been the central tool of clinical geneticists, used to identify clues about diagnoses or risk factors for patients. It is likely that other healthcare providers will look to the family history to determine who is at increased risk for a condition, what testing and management options are appropriate based on the history, and who may benefit from additional genetic services.

Medical Family History Competencies

Based on competencies in medical genetics published by various professional organizations, such as APHMG/ASHG (2001), it appears that obtaining a thorough medical family history has become a routine expectation in medical practice (Tarini & McInerney 2013).

- All health professionals should understand the importance of family history (minimum 3 generations) in assessing predisposition to disease.
- All health professionals should be able to gather genetic family-history information, including an appropriate multigenerational family history.

(NCHPEG 2000)

FAMILY HISTORY AND PRIMARY CARE

Family History and Primary Care

Most physicians obtain some family history information from patients, most commonly by way of a checklist on a screening questionnaire or brief interview. However, this limited information will likely

be insufficient to reliably identify individuals who may benefit from advances in genetic medicine. Rich et al. (2004) recently reviewed the barriers to incorporating a more thorough family history into the primary care visit. These included time constraints, limited reimbursement for such services, and physicians' self-reported concerns about inadequate training to successfully implement the family history.

Training Barrier

Certainly, educational programs such as this CE course can address the training barrier, but time constraints and reimbursement issues are more problematic. Family history programs that speed the collection of relevant data and provide some intelligent decision-making support based on the information may be the ideal solution. However, after review of currently available tools -- such as paper-based family history screening forms, automated pedigree drawing programs, family history components of electronic medical record programs, and risk assessment programs for very specific indications -- Rich et al. (2004) identified no existing tools deemed to be ideal solutions (as defined below). Furthermore, the authors state, "Unfortunately, such tools are years in the future, but primary care physicians must wisely collect and use family history information today" (Rich et al. 2004).

Components of the Ideal Family History Tool

- Completed by the patient
- Understandable (based on patient's language and educational level) and easy to use
- Available in multiple different medias (paper, Web-based)
- Compatible with multiple currently used information management systems (electronic medical records, personal digital assistants)
- Branches and prioritizes based on clinical significance
- Provides clinical decision-making support (risk assessment, management recommendations)

(Adapted from Rich et al. 2004, Table 4)

MEDICAL FAMILY HISTORY SCREENING TOOLS

Medical Family History Screening Tools

Triaging patients who require a more detailed family history through the use of a suitable paper-based medical family-history screening form is a viable solution until consensus is reached about the best approach in primary care (Rich et al., 2004). Some of the available screening forms that you may consider using in your practice are listed in the Related Resources section.

Current family history screening tools exist as patient-completed screening questionnaires and more general instruction for patients or providers on how to create an individual family history or pedigree. Because the risk assessment information required may vary considerably based on the indication, screening forms are often specialized. Here, we categorize screening forms as most appropriate for:

- General
- Adult
- Preconception/prenatal
- Pediatric populations

In primary care, several different forms, depending on the age and circumstances of your patients, may need to be used. Another source of information about available screening tools is the National Coalition for Health Professional Education in Genetics (NCHPEG) Family History Working Group, which plans to systematically review family history tools and resources for use in teaching and clinical practice in its newsletter The Genetic Family History in Practice

A relatively new tool was introduced in fall 2004 through the US Surgeon General's Family History Initiative. The Surgeon General's office provides My Family Health Portrait from the Centers for Disease Control and Prevention is an internet-based tool that makes it easy for patients to record family health history. The tool is easy to access on the web and simple to fill out. It takes about 15 to 20 minutes to build a basic family health history. The tool generates a pedigree and family health history form that patients can print out and share with their health provider. However, it should be noted that this form will only assess risk for specific common disorders and will potentially miss important inherited conditions.

Family History and Public Health

The Centers for Disease Control and Prevention (CDC) is involved in a public health initiative to determine if a family history tool can be used as an effective method for assessing common disease risk and influencing prevention (Yoon, 2002). The screening tool is designed for the patient to complete on a home or physician's office computer and is primarily envisioned for use in the primary care setting. Using a series of risk algorithms, an assessment of average, moderate, or high risk would be predicted for specific diseases. Management strategies would be suggested for the patient and managing primary care physician.

Learn more about this initiative.

The criteria that the CDC used to select disorders for inclusion in the family history tool included the following:

- Substantial public health burden
- Well-defined diagnostic criteria
- Awareness of disease among relatives
- Accurately reported by family members
- Family history is an established risk factor
- Effective prevention strategies exist

(Yoon 2003)

Based on the above criteria, the CDC has chosen the following 6 diseases to include in the prototype tool and will add others as they are validated:

- Heart disease
- Stroke
- Diabetes
- Breast cancer
- Ovarian cancer
- Colon cancer

(CDC 2004)

The family history tool will be designed to be:

- Simple, easily applied, and inexpensive
- Capable of reliably defining those at moderate and high risk for a disorder
- Used in combination with other risk factors
- Useful for targeting interventions and positively influencing health behaviors without undue harm or cost
- Amenable to population-based screening

(CDC 2004)

Risk and associated recommendations will be classified as:

- **Average:** standard public health recommendations
- **Above average:** personalized prevention recommendations
- **Much above average:** personalized prevention recommendations and genetics evaluation referral

(CDC 2004)

The family history tool prototype, Family Healthware, is currently being pilot tested. The CDC awarded funding to 3 primary care clinic sites in 2003 for evaluation. Once ready for widespread application, the program is expected to be available as both a CD-ROM and an Internet-based application, although other formats are being considered (paper forms, in-office touch screen kiosks). An electronic resource manual will be provided to guide physicians in interpreting risk levels and determining appropriate preventive measures (CDC 2004).

MAKING THE CASE FOR THE PEDIGREE

Making the Case for the Pedigree

Once you have decided that a more comprehensive medical family history is indicated for a patient, you could document the information in text format; but consider the benefits of adopting the pedigree approach. The pedigree, or family tree, is a graphical representation of the family using symbols and relationship lines, not unlike the genogram sometimes used in family medicine and other disciplines. Once some basic nomenclature and symbols are mastered, the pedigree becomes an expeditious, concise, accurate, and visually obvious representation of a family's relationships and medical history.

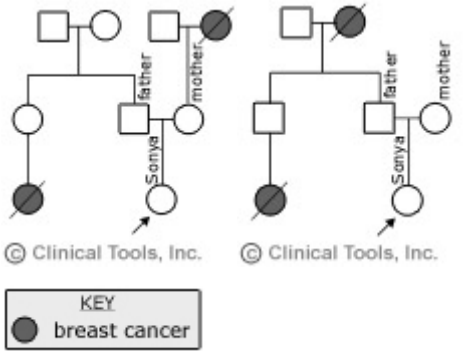
The Patient's Medical Record

Consider this chart note from a patient's medical record:

"Sonya's grandmother and cousin died of breast cancer."

When evaluating a family history of breast cancer, factors such as how many family members are affected, how they are related to each other, and how they are related to your patient are critical. The following pedigrees are from 2 families that are both consistent with the above description but have very different risk implications.

Pedigree 1 and Pedigree 2:



View pedigree symbols legend

A brief glance indicates that Pedigree 1 is much less suspicious for a hereditary breast and ovarian cancer gene mutation (BRCA1 or BRCA2) than the second. In Pedigree 2, the 2 affected family members are biologically related to each other, and they are related through a male who is less likely to manifest breast cancer if he does have a BRCA mutation. Sonya is also related to the 2 affected women through a male, her father.

To accurately describe these relationships in text form is somewhat cumbersome:

Pedigree 1: Sonya's paternal female first cousin (related to Sonya through an unaffected aunt) died of breast cancer. Her maternal grandmother also died of breast cancer.

Pedigree 2: Sonya's paternal grandmother and female paternal first cousin (related to Sonya through an unaffected uncle) died of breast cancer.

(Example adapted from Bennett 2010)

Uses of the Pedigree

- Documentation
- Diagnosis
- Risk assessment
- Management

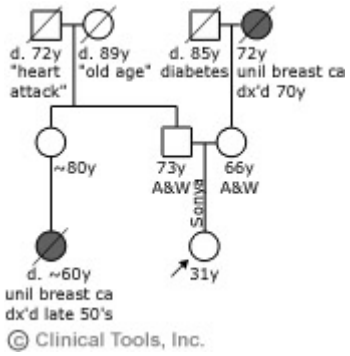
To learn more about documentation, diagnosis, risk assessment, and management with a pedigree,review pedigree uses.

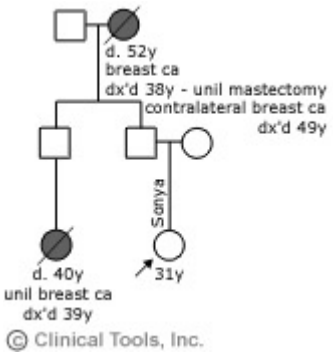
ADDITIONAL BENEFITS OF THE PEDIGREE

Additional Benefits of the Pedigree

Now consider that medical information, such as age at diagnosis, unilateral as compared to bilateral disease, multiple primary cancers, and history of other forms of cancer, is critical for each affected family member.

Pedigree 1: **Pedigree 2:** View pedigree symbols legend

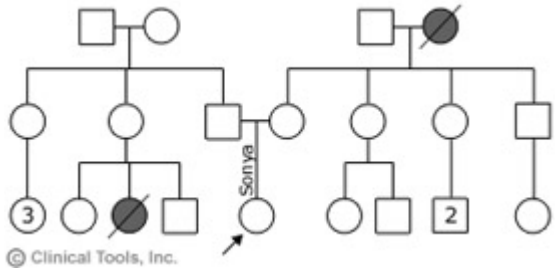




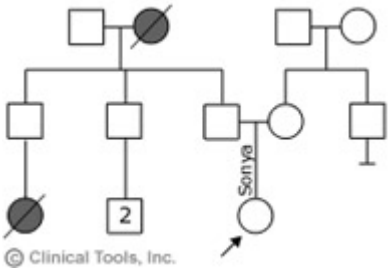
Unaffected Family Members

And the number and gender of unaffected family members is also important in risk interpretation and identification of other at-risk family members.

Pedigree 1:



Pedigree 2:



View pedigree symbols legend

It quickly becomes apparent that the pedigree offers superior documentation compared to a narrative chart note.

(Example adapted from Bennett, 2010)

Other Benefits

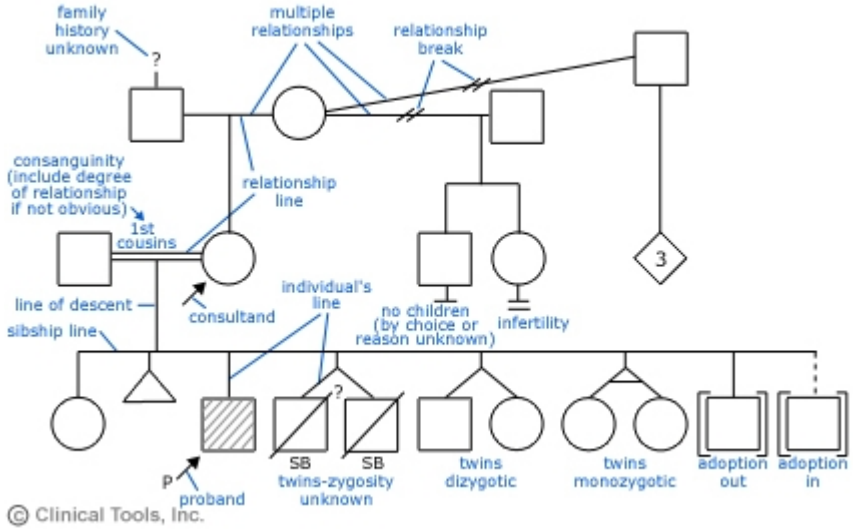
Some other benefits of maintaining a dedicated pedigree to record your patients' medical family histories include the following:

- The pedigree is easily updated with new medical information. This allows you to recognize emerging patterns that may be missed when the information is kept in pieces scattered throughout the chart notes.
- Once a diagnosis or risk has been identified, a pedigree makes it straightforward to identify other at-risk family members.
- The pedigree can be easily extracted from the chart if it becomes desirable to separate clinical medical information from genetic information (such as to preserve patient and/or family member privacy and confidentiality).

THE LANGUAGE OF THE PEDIGREE

The Language of the Pedigree

The pedigree shorthand language is most useful when it can be interpreted by any healthcare provider. Historically, many different pedigree "languages" have been used. However, in 1995 the National Society of Genetic Counselors' (NSGC) Pedigree Standardization Task Force published standard pedigree nomenclature and symbols developed through a peer-reviewed process (Bennett et al. 1995; Bennett et al. 2008) that have been widely adopted. Some of the most widely used symbols are shown in the figure to the right. The standard nomenclature for relationships and other special circumstances are shown in the example pedigree below.



ADDITIONAL PEDIGREE INSTRUCTION

Additional Pedigree Instruction

This activity is optional and can only be viewed on non-mobile devices and devices enabling flash

If you would like additional instruction about constructing a pedigree, consider completing our "A Royal Pedigree" activity (about 15 to 30 minutes). This activity demonstrates how a pedigree is built, while telling the story of the impact that genetics has played in the history of Europe's royal families. Note that this activity has not been approved for continuing education credit and is not included in the total number of possible hours.

We recommend that you complete each of the following **four** sections in order by clicking on the titles. This will open the Flash movie. If you are quite comfortable with basic pedigree symbols and nomenclature, you may consider skipping the first section (although this provides some background information about the Royal Family's relationships).

(Clinical Tools Inc., 2008)

CASE HISTORY

Introduction

Being able to draw the pedigree is obviously just the first step in successfully taking and assessing a family history. In this section, you will observe a family history being taken for a typical patient that you may encounter in any primary care setting. You will have an opportunity to evaluate the family history for any red flags, probe more deeply where indicated, and determine appropriate management strategies based on the findings.

Consider drawing the pedigree as the facts are disclosed. You can print a blank pedigree form to fill in if you like.

Maria's First Visit

Maria is being seen by Dr. Walters today for the first time. She and her husband recently moved to the area due to a change in jobs. Maria was referred to the practice by a coworker when she mentioned that she needed to find a new primary care physician. Maria is scheduled for a routine physical.

When Maria arrives at the office, the receptionist gives her the office's standard medical history form to complete. The receptionist also explains that Dr. Walters asks all of her patients that are of reproductive age to complete the March of Dimes' preconception screening form. She explains that the form is voluntary; but if there is any possibility that Maria could become pregnant, the form could help identify any issues that Maria should know about if she were to become pregnant.

Maria and her husband have been married for over a year and have recently begun to talk about getting pregnant. While she hadn't previously considered whether or not she had any reproductive concerns, Maria was interested in what the screening form may uncover and any recommendations Dr. Walters may have.

Tools

The following tools may be used throughout the case study to reference as needed.

Family History Red Flags

Individuals with findings that are uncommon or who have unusual presentations of common disorders should cause you to consider a genetic etiology and referral. Some examples of red flags in the medical family history are shown below.

The following are general red flags:

- Multiple family members with the same condition
- Familial "clustering" of cancers that may have the same etiology (colorectal cancer and endometrial cancer due to HNPCC mutation)
- Ethnicity known to be associated with increased risk for specific genetic conditions (sickle cell among those of African descent, BRCA mutations more common in Ashkenazi Jewish individuals)
- Consanguinity

Any individual with the following:

- Birth defects

        - isolated major congenital anomalies (cleft lip, congenital cardiac defects)
        - combinations of major and/or minor anomalies (extra digits, widely spaced eyes)
            - 2 or more major anomalies
            - 3 or more minor anomalies
            - 1 major and 2 minor anomalies
- Mental retardation/developmental delay, especially if
    - unexplained
    - progressive
    - associated with dysmorphic features, physical anomalies, or unusual medical conditions
- Other unusual physical findings
    - dysmorphic features
    - abnormal pigmentation (particularly if associated with other abnormal findings)
    - significant short stature
- A recognized single-gene (cystic fibrosis, muscular dystrophy) or chromosomal (Down syndrome, translocation) disorder
- Congenital or early-onset deafness or blindness
- Unexplained neuromuscular conditions, particularly with early onset (movement disorders, ataxia, hypotonia, seizures)
- Symptoms suspicious for metabolic disease
    - neonatal deaths/SIDS
    - failure to thrive
    - loss of developmental milestones
    - unusual odors
- Reproductive abnormalities
    - abnormal development: ambiguous genitalia, primary amenorrhea, hypogonadism
    - infertility: oligospermia or azoospermia, congenital absence of the vas deferens, premature ovarian failure
    - recurrent pregnancy loss (generally defined as 3 or more miscarriages or stillbirths)
- Common conditions
    - with an unusual presentation
        - an earlier age of onset than usual (colorectal cancer at 40 years, dementia at 50 years)
        - more severe course than usual
        - combined with other typically unrelated findings or dysmorphic features
        - multiple primary cancers in a single person
        - bilateral disease in paired organs
    - that appear to be "running in the family," particularly if suspicious for a single-gene pattern of inheritance (mental illness, diabetes)
- Rare cancers/tumors
- Sudden premature death in an apparently healthy person

(Adapted from Bennett 2010)

Of course, the types of findings that are currently significant to your patient may vary depending on the presenting indication. For instance, a known or suspicious family history of cystic fibrosis will likely

warrant more consideration for a patient who could become pregnant when compared to an individual in his or her 50s with no symptoms suggestive of respiratory or pancreatic disease. However, once you recognize a potential genetic risk, you do the family a great service in discussing potential implications and genetics referral, even if they are not immediate concerns for your patient.

Pedigree Components

Major Components

- Consultant: person requesting services or asking questions
- Historian(s): person(s) providing the family history
- Recorder: person recording the family history
- Date the pedigree was taken or updated
- Minimum of 3 generations of family members; may be more based on indication or identified red flags (children, parents, siblings, grandparents, aunts/uncles, cousins)
- Age and birth date (or year) for all individuals
- Names (or initials when privacy is an issue) for easy reference, medical records request, etc. for all individuals
- Ethnic background for each of the 4 grandparents ("Do you know what country your ancestors originally came from?")
- Consanguinity ("Has anyone in your family had children with a biological or blood relative?"): record "denied" or show on pedigree with relationship if not implicit
- Exposure history when indicated (preconception/prenatal, personal or family history of cancer or other disease): occupation, medications, recreational drug and alcohol use, etc.
- Specifically ask if anyone in the family has had a child with a birth defect, mental retardation, or known genetic condition
- Specifically inquire about miscarriages, stillbirths, and neonatal deaths
- Specifically inquire about cancers in the family

Specific Circumstances

- **Significant medical history:** appropriately shade symbol and define in key; record age at diagnosis and relevant medical information (see targeted question lists by indication)
- **Ongoing pregnancies:** record gestational age, LMP, and/or EDC
- **Pregnancy losses:** use appropriate symbol and note gestational age, any etiology information, and if SAb (miscarriage), SB (stillbirth), TOP (termination), or ECT (ectopic)
- **Reproductive age individuals without children:** inquire if by choice or infertility
- **Deceased individuals:** age at death and cause of death
- **Healthy people with no findings of medical significance:** specifically note "A&W" (alive and well)
- **Unclear or uncertain family medical information (hearsay, family myths):** place information in quotes without assuming meaning or interpreting the actual medical facts yourself
- **Unknown or unavailable history:** place a "?" above their symbol

Remember

- Confirm siblings share the same mother and father
- Remind family that you are interested in deceased relatives, too

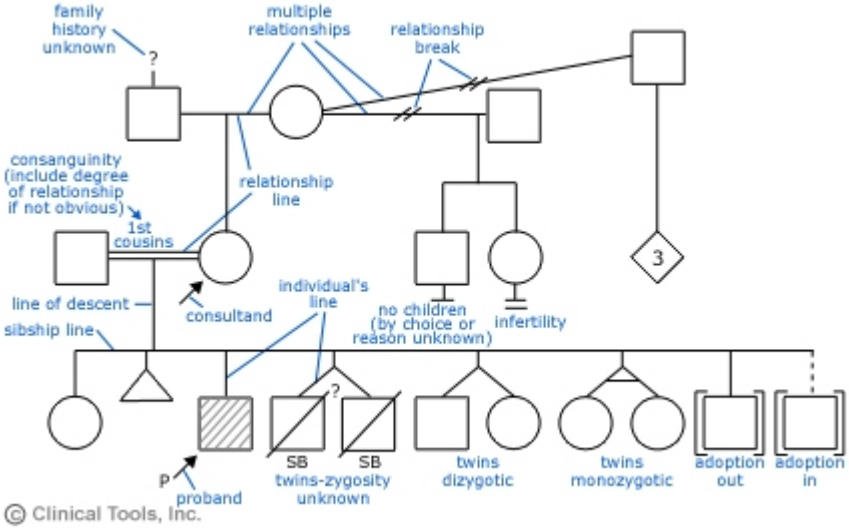
- Define abbreviations in a legend
- Avoid leading questions ("So everyone is healthy?" vs. "Is everyone healthy?")
- Avoid value-laden terminology ("abnormal," "bad")
- Other questions may be appropriate based on indication (exposure history in preconception/prenatal counseling)

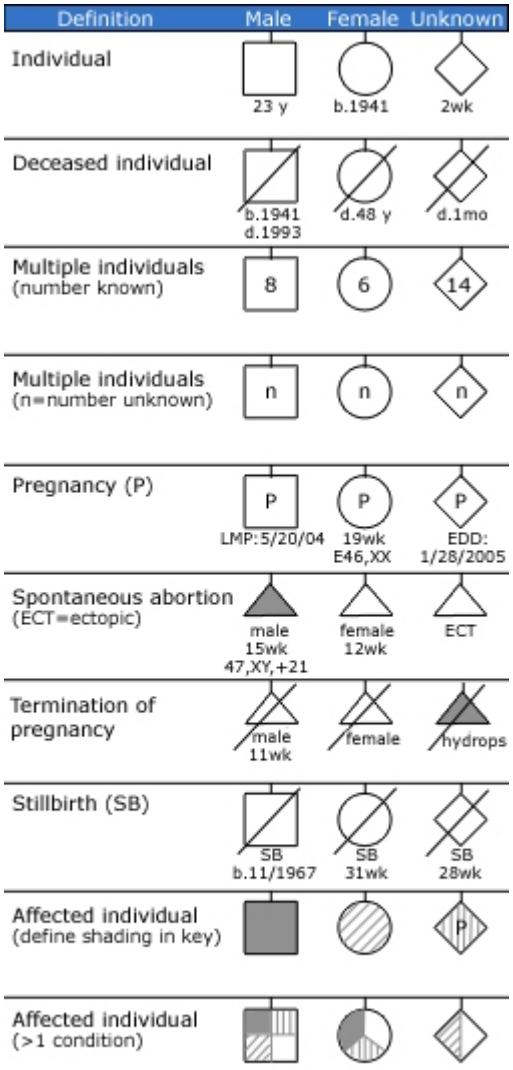
In Closing

- Does anyone else in your family have health problems or any unusual physical features that we haven't talked about?
- Is there anything that seems to run in your family?
- Is there anything else that you are concerned about that we haven't discussed?
- Is there anything else that you think is important for me to know?

(Adapted from Bennett 2010)

Pedigree symbols





Adapted from Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. /Am J Hum Genet./ 1995;56:745-52.

PRECONCEPTION PLANNING

All pregnancies can benefit from preconception planning. There may be a positive family history to explore, exposures that should be minimized or avoided, screening based on ethnicity to consider, or simply additional folic acid needs to reduce the risk of neural tube defects.

However, about half of pregnancies are unplanned (CDC 2013). Significant fetal development has already occurred by the time a pregnancy is recognized, and the option of some potentially beneficial interventions is lost. The possibility of pregnancy should be considered for any reproductive-age woman, and appropriate screening and education provided.

ASSESS SCREENING FORM

Assess Screening Form

From her screening form, we learn that Maria is a 27-year-old woman with no previous pregnancies and no concerning personal medical history. Her husband, Joe, is 29 years old, in good health, and was adopted.

Maria	***Joe***	
Date of birth	6-16-77	11-2-75
Occupation	Real estate agent	Police detective
Last grade completed	11th/GED	College
Height	5'2"	5'10"
Weight	145 lbs	170 lbs
Adopted	No	Yes
Ethnicity	European Caucasian; African/African-American; Hispanic	Hispanic?

The significant family history information is excerpted below

Maria's Family	***Joe's Family***	***Who Is Affected?***
Congenital heart defect (i.e., "hole" in the heart)	X	Cousin
Mental retardation or developmental delay	X	Cousin
Down syndrome or other chromosome syndrome	X	Cousin
High blood pressure or hypertension	X	Father
Other cancers or tumors	X	Aunt
Infant or childhood deaths	X	Cousin
Two or more miscarriages or pregnancy losses (in the same person)	X	Sister-in-law
Are you and your partner/spouse related as first cousins or in any other way as blood relatives?	No	

(Adapted from March of Dimes)

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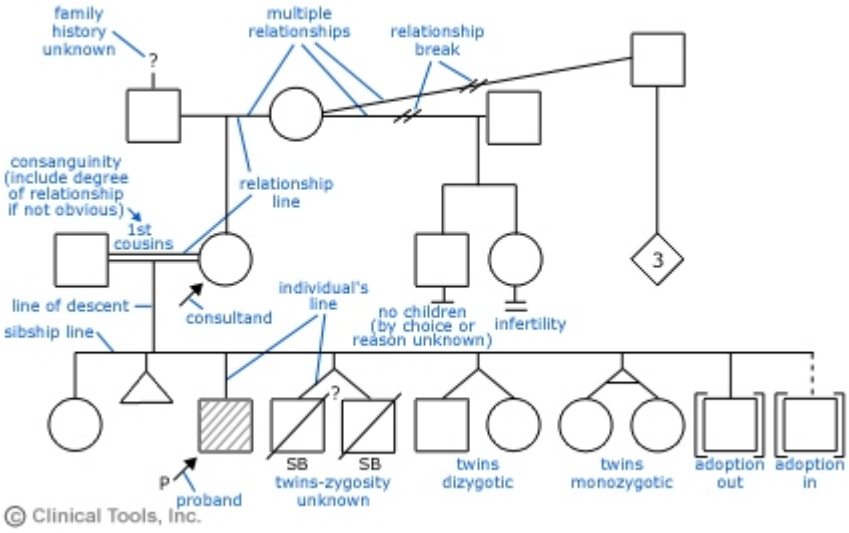

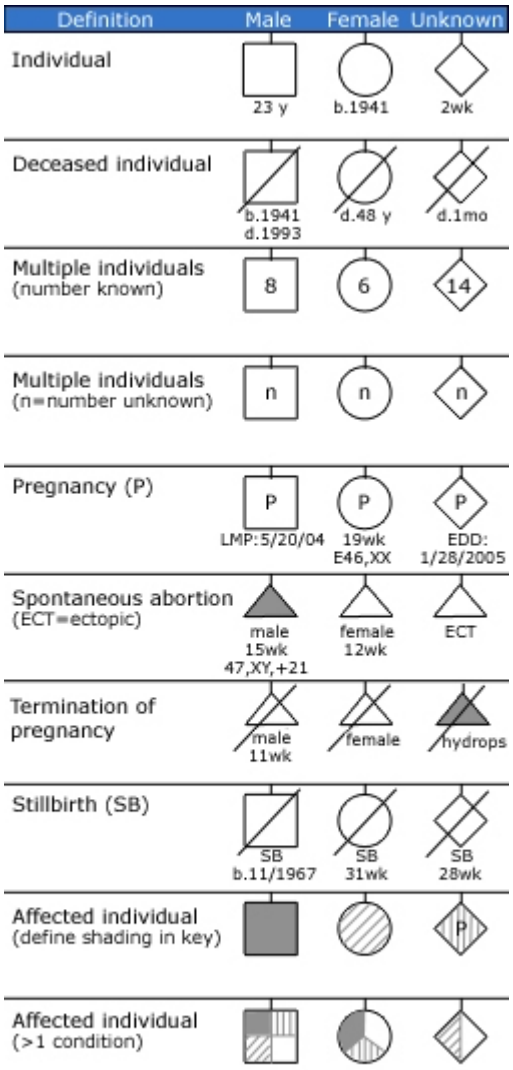

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PEDIGREE TOOLS

Family History Red Flags

In order for the genetic family history to be a useful tool, the clinician must recognize from a genetics perspective those findings most likely to be significant. In general, some combination of common disorders will be seen in most families. Findings that are uncommon or unusual presentations of common disorders should cause you to consider a genetic etiology and referral. When uncertain, it is always best to consult a genetics professional. Please note the 'Family Red Flags' in the 'Tools' section for a more complete list.

Pedigree Components

Certain information is essential to record on a family history pedigree, which includes:

- Age
- Cause of death
- Siblings vs half siblings
- Pregnancies
- Ethnic background
- First names (if appropriate, noting privacy)
- The recorder/historian name

(Adapted from Bennett 1999, Table 3.1)

Refer to 'Pedigree Components' in the 'Tools' section for a complete list of information routinely included in the pedigree.

Pedigree symbols

Many symbols are used in the family history pedigree including symbols for:

- Individuals
- Deceased
- Pregnancy
- Affected individuals

For guidance in recognizing these families, please refer to our lists located in the "Tools" section. The "Tools" section contains information about each of the topics described here and will appear on each page for your reference.

Tools

The following tools may be used throughout the case study to reference as needed.

Family History Red Flags

Individuals with findings that are uncommon or who have unusual presentations of common disorders should cause you to consider a genetic etiology and referral. Some examples of red flags in the medical family history are shown below.

The following are general red flags:

- Multiple family members with the same condition
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- Ethnicity known to be associated with increased risk for specific genetic conditions (sickle cell among those of African descent, BRCA mutations more common in Ashkenazi Jewish individuals)
- Consanguinity

Any individual with the following:

- Birth defects
    - isolated major congenital anomalies (cleft lip, congenital cardiac defects)
    - combinations of major and/or minor anomalies (extra digits, widely spaced eyes)
        - 2 or more major anomalies
        - 3 or more minor anomalies
        - 1 major and 2 minor anomalies

- Mental retardation/developmental delay, especially if
    - unexplained
    - progressive
    - associated with dysmorphic features, physical anomalies, or unusual medical conditions
- Other unusual physical findings
    - dysmorphic features
    - abnormal pigmentation (particularly if associated with other abnormal findings)
    - significant short stature
- A recognized single-gene (cystic fibrosis, muscular dystrophy) or chromosomal (Down syndrome, translocation) disorder
- Congenital or early-onset deafness or blindness
- Unexplained neuromuscular conditions, particularly with early onset (movement disorders, ataxia, hypotonia, seizures)
- Symptoms suspicious for metabolic disease
    - neonatal deaths/SIDS
    - failure to thrive
    - loss of developmental milestones
    - unusual odors
- Reproductive abnormalities
    - abnormal development: ambiguous genitalia, primary amenorrhea, hypogonadism
    - infertility: oligospermia or azoospermia, congenital absence of the vas deferens, premature ovarian failure
    - recurrent pregnancy loss (generally defined as 3 or more miscarriages or stillbirths)
- Common conditions
    - with an unusual presentation
        - an earlier age of onset than usual (colorectal cancer at 40 years, dementia at 50 years)
        - more severe course than usual
        - combined with other typically unrelated findings or dysmorphic features
        - multiple primary cancers in a single person
        - bilateral disease in paired organs
    - that appear to be "running in the family," particularly if suspicious for a single-gene pattern of inheritance (mental illness, diabetes)
- Rare cancers/tumors
- Sudden premature death in an apparently healthy person

(Adapted from Bennett 2010)

Of course, the types of findings that are currently significant to your patient may vary depending on the presenting indication. For instance, a known or suspicious family history of cystic fibrosis will likely warrant more consideration for a patient who could become pregnant when compared to an individual in his or her 50s with no symptoms suggestive of respiratory or pancreatic disease. However, once you recognize a potential genetic risk, you do the family a great service in discussing potential implications and genetics referral, even if they are not immediate concerns for your patient.

Pedigree Components

Major Components

- Consultant: person requesting services or asking questions
- Historian(s): person(s) providing the family history
- Recorder: person recording the family history
- Date the pedigree was taken or updated
- Minimum of 3 generations of family members; may be more based on indication or identified red flags (children, parents, siblings, grandparents, aunts/uncles, cousins)
- Age and birth date (or year) for all individuals
- Names (or initials when privacy is an issue) for easy reference, medical records request, etc. for all individuals
- Ethnic background for each of the 4 grandparents ("Do you know what country your ancestors originally came from?")
- Consanguinity ("Has anyone in your family had children with a biological or blood relative?"): record "denied" or show on pedigree with relationship if not implicit
- Exposure history when indicated (preconception/prenatal, personal or family history of cancer or other disease): occupation, medications, recreational drug and alcohol use, etc.
- Specifically ask if anyone in the family has had a child with a birth defect, mental retardation, or known genetic condition
- Specifically inquire about miscarriages, stillbirths, and neonatal deaths
- Specifically inquire about cancers in the family

Specific Circumstances

- **Significant medical history:** appropriately shade symbol and define in key; record age at diagnosis and relevant medical information (see targeted question lists by indication)
- **Ongoing pregnancies:** record gestational age, LMP, and/or EDC
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Remember

- Confirm siblings share the same mother and father
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- Define abbreviations in a legend
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In Closing

- Does anyone else in your family have health problems or any unusual physical features that we haven't talked about?
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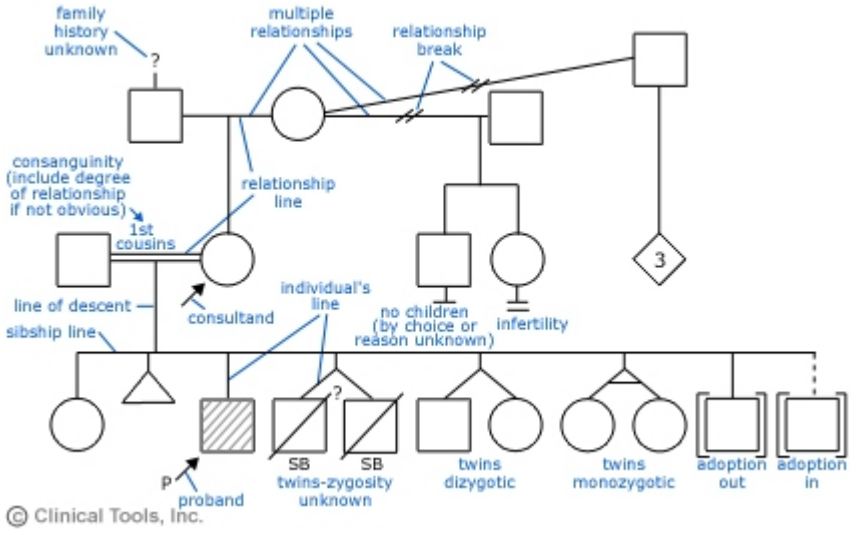

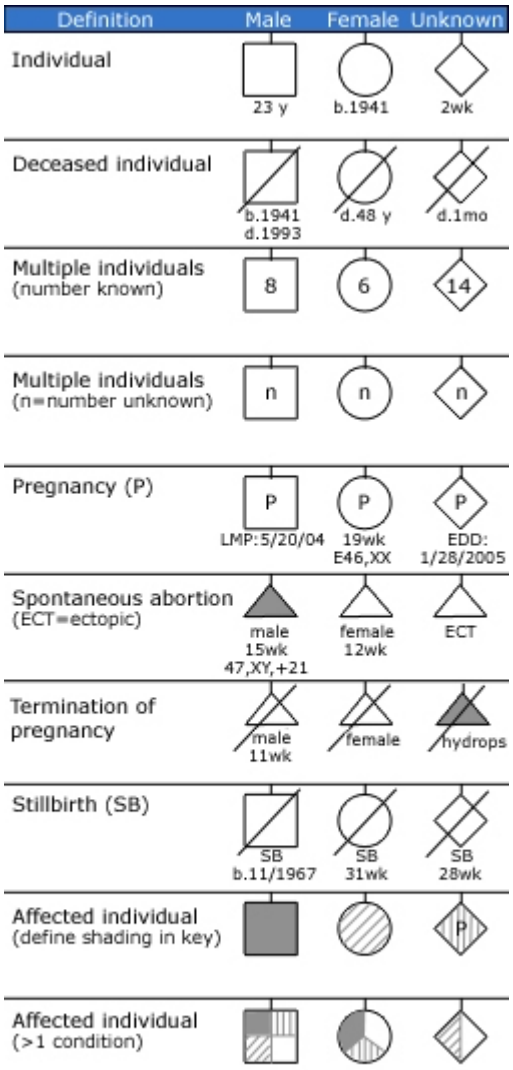

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MARIA'S PERSONAL MEDICAL HISTORY

Maria's Personal Medical History

Doctor: I've looked over the health history form you filled out, but I would like to know what your primary concerns are today. [Beginning the session by asking the patient's concerns helps to assure that the clinician meets the patient's expectations.]

Maria: We just moved to this area and I wanted to get connected with a doctor. I feel like I'm healthy, but I just want to make sure because my husband and I are ready to plan our family. We've been married a year and we think it is time. My sister-in-law just had her third miscarriage. I also had a cousin with some kind of birth defect. Maybe it was Down syndrome -- I don't really know for sure. I didn't grow up near them. I just hope I don't have anything like this to worry about.

Doctor: Okay. First let me ask you some questions about your family's health history. Then I'll examine you.

I am going to draw a family chart or pedigree to help me sort through any medical problems that may occur in your family that might be important to know about. [Explaining what will happen in the session helps clarify what will be covered.]

First, let's start with you. So, you are 27 years old. Tell me a little bit about what you do. Do you work outside the home?

Maria: I work as a real estate agent.

Doctor: That sounds interesting. How far did you go in school?

Maria: Well, I got my GED and then my real estate license.

Doctor: Did you have any special classes in school or did you have any problems learning? [Asking this question helps determine if Maria had any learning disabilities.]

Maria: Not really, I could have applied myself more, but I really didn't have problems with any of the work.

Doctor: How about your overall health -- do you have any major health problems?

Maria: No. I had the usual childhood illnesses like ear infections and chicken pox. I really try to watch my diet and exercise.

Doctor: Have you had any surgeries or hospitalizations?

Maria: No. I broke my arm once playing soccer.

Doctor: How about alcohol? How much do you drink?

Maria: Oh, not very much.

Doctor: How much? Do you drink every day? What do you like to drink? [Never assume that you know how much alcohol is a lot. Patients will tend to report less than they actually drink. It is better to overestimate -- for example, "Do you drink 6 drinks a day?" The same is true for tobacco use and street drugs.]

Maria: [Laughs] Oh, no. I maybe have 1 or 2 beers on the weekend or if we are on vacation.

Doctor: How about tobacco? Do you smoke cigarettes?

Maria: I smoked for a while after high school. But I haven't had a cigarette in 4 years.

Doctor: Good for you. It is important that you not smoke. How about street drugs?

Maria: Mmm. Well, I smoked dope a few times, but that was a long time ago.

Doctor: It sounds like you've made a lot of positive changes in your life. Have you ever been pregnant?

Maria: No. We stopped using birth control about 3 months ago because we really hope I can get pregnant sometime this year.

Tools

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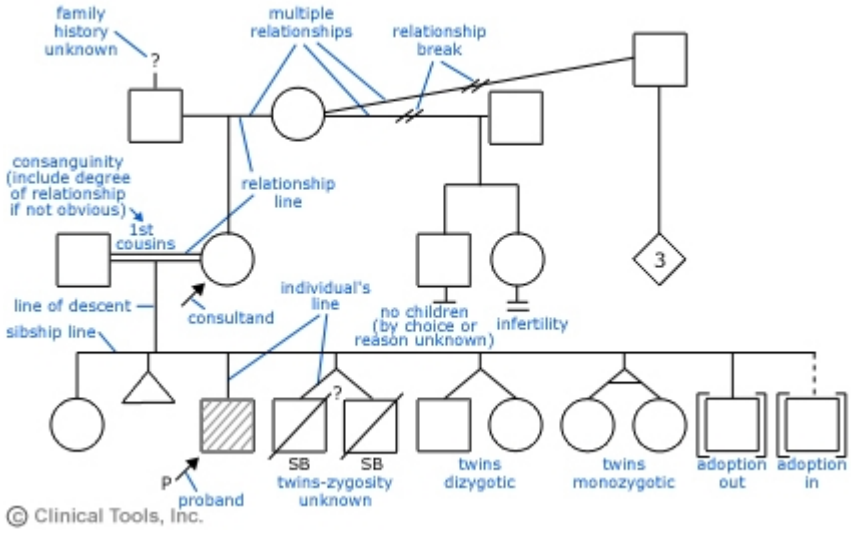

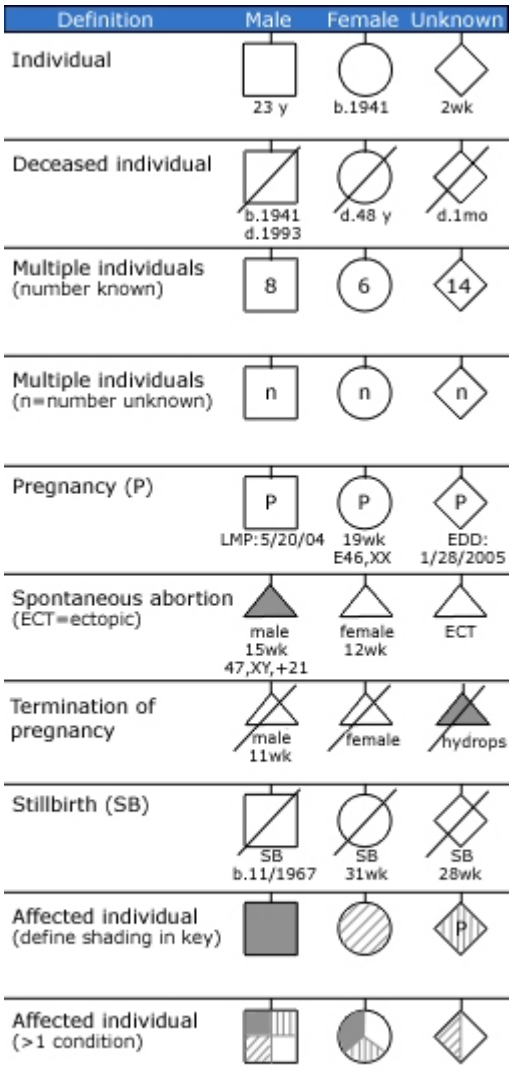

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BEGIN MARIA'S FAMILY HISTORY

Begin Maria's Family History

Doctor: It can often take up to a year to get pregnant, even when you both are healthy. Now, I'd like to ask some questions about your family. Do you have any brothers or sisters?

Maria: I just have one brother.

Doctor: How old is he? And is he a full brother -- does he have the same mother and father as you?

Maria: Yes, he does. He is 25. But I forgot -- many years ago, my father had a child with his first wife. The baby died soon after birth. I think it was a boy; I'm not sure. My dad really never talked about it much.

Doctor: Did anyone in your family ever talk about an explanation for why the baby may have died?

Maria: Not that I remember.

Doctor: Do you know if they ever did an autopsy on this baby? It would be helpful to know more about why the baby didn't survive.

Maria: I don't know. I could ask my dad.

Doctor: That would be good. If the baby died in the United States, a death certificate could also be helpful. [Obtaining death certificates often includes other information besides the cause of death -- for example, other underlying health problems and the name of the medical center so that medical records can be obtained through properly signed medical releases.]Did your father and his first wife have any other children together?

Maria: No, they weren't together very long. I always wondered if losing the baby had anything to do with that.

Doctor: Losing a baby can certainly be hard on any relationship. Has anyone else had any pregnancy losses or babies that didn't survive?

Maria: Well, my brother's wife has had 3 miscarriages in the last 3 years. They are really worried. It worries me, too.

Tools

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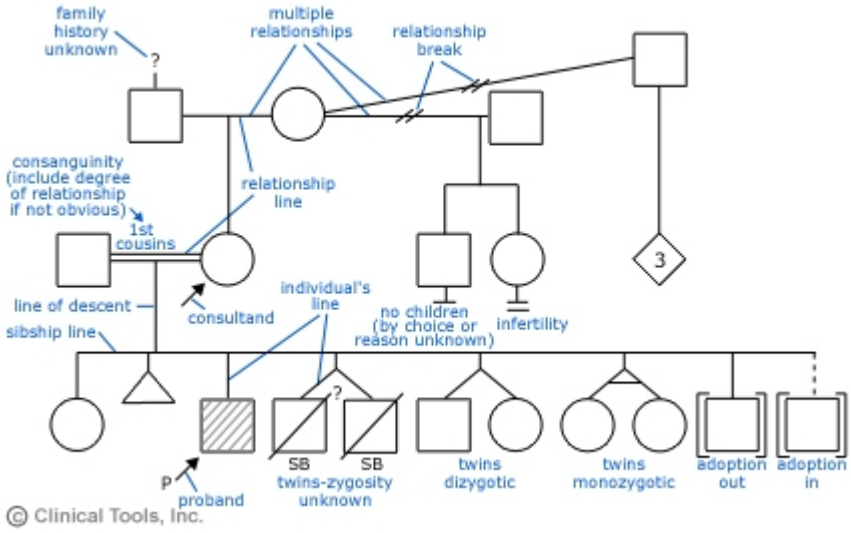

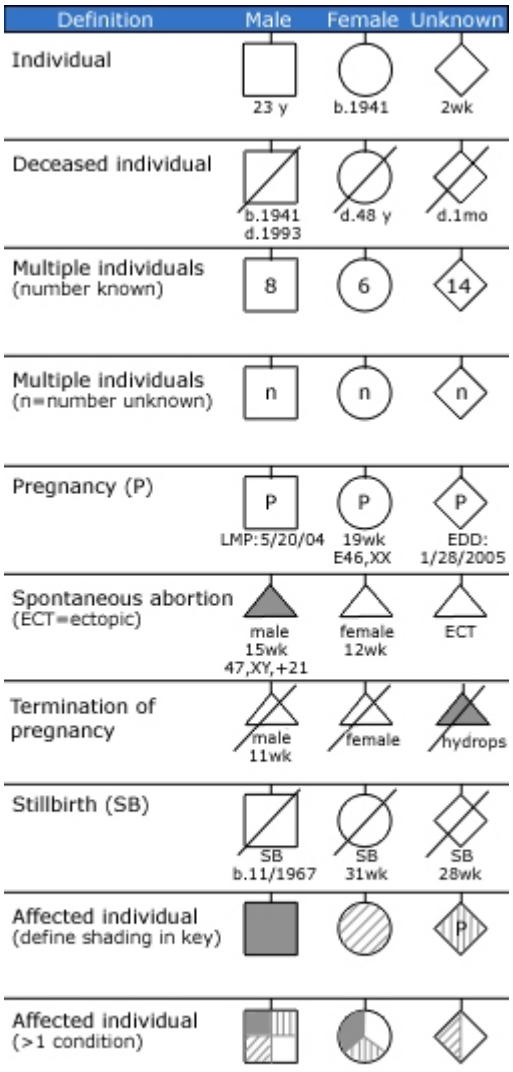

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CONTINUE RECURRENT PREGNANCY LOSS FAMILY HISTORY CONVERSATION

Pedigree Check

Click on the link to Maria's History in the Related Resources section to review the family history as it currently stands and to compare it to your own version before proceeding.

Talking to the Patient

Doctor: I'm sure that the miscarriages are hard for you and for them. Do you know if they have had a medical evaluation or any testing to help determine why they have had these miscarriages? [Acknowledging difficult situations such as pregnancy loss or death helps to develop rapport.]

Maria: I'm not sure. I think they are planning to see someone now that she has had so many miscarriages.

Doctor: Hopefully that will help them get some answers. Do you know how far along she was in each pregnancy?

Maria: Not exactly -- it was early. A couple of them we didn't even know she was pregnant yet.

Doctor: Unfortunately miscarriages are common, especially in the first trimester, but sometimes there are genetic reasons that miscarriages occur. Has anyone else in your family had a miscarriage or a baby who died?

Maria: Actually, my mother had a miscarriage between having me and my brother. I don't think anyone else did. But I mentioned that my dad had a baby who died a long time ago. And then there is my cousin who had a heart defect and other problems. She died when she was about a year old. Do you think this is all related?

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Of course, the types of findings that are currently significant to your patient may vary depending on the presenting indication. For instance, a known or suspicious family history of cystic fibrosis will likely warrant more consideration for a patient who could become pregnant when compared to an individual in his or her 50s with no symptoms suggestive of respiratory or pancreatic disease. However, once you recognize a potential genetic risk, you do the family a great service in discussing potential implications and genetics referral, even if they are not immediate concerns for your patient.

Pedigree Components

Major Components

- Consultant: person requesting services or asking questions
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- Minimum of 3 generations of family members; may be more based on indication or identified red flags (children, parents, siblings, grandparents, aunts/uncles, cousins)
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Remember

- Confirm siblings share the same mother and father
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In Closing

- Does anyone else in your family have health problems or any unusual physical features that we haven't talked about?
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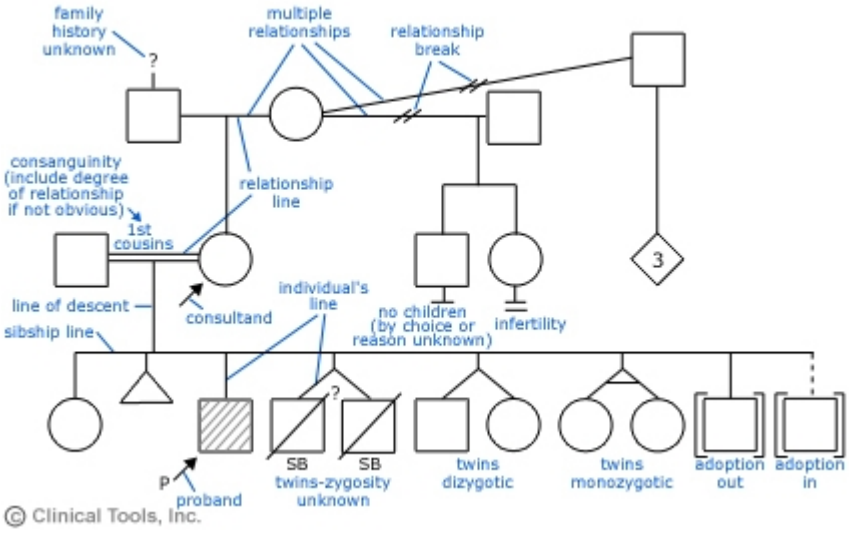

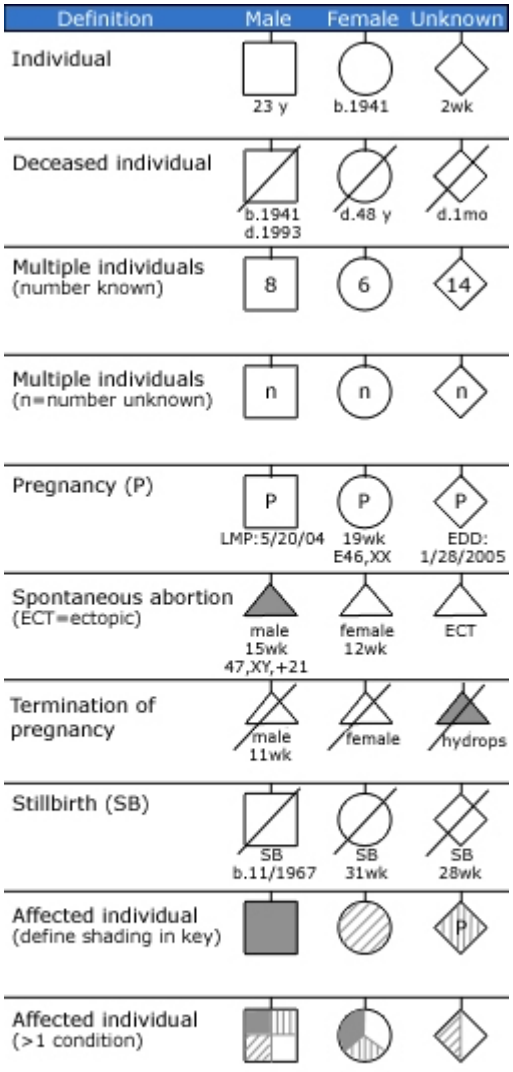

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CONTINUE MARIA'S PATERNAL FAMILY HISTORY

Continue Maria's Paternal Family History

Doctor: It could all be related, but it's hard to say without knowing more about why these things happened. Let's step back a minute and get all this information down, and then we can talk more about what it might mean. How old is your father, and does he have any health problems?

Maria: Not really -- he has high blood pressure. He is 50. Otherwise he is in good health.

Doctor: How many brothers and sisters does he have? And do all of them have the same mother and father?

Maria: Well, he has 2 sisters. And, yeah, they're not half sisters or anything. His one sister is 49 and the other is 45.

Doctor: How about his 49-year-old sister? How is her health?

Maria: Oh, she is really healthy. She has 2 sons who are living. She also had the daughter, my cousin, who had birth defects. I don't think that baby's development was normal. I didn't grow up near them, though, and since she didn't live that long, I don't really know a lot about her.

Doctor: Have you ever seen a picture of her daughter, your cousin?

Maria: Yes.

Doctor: When you look at the picture, can you tell if something is unusual just from her picture? Does she look like other members of your family? [Family photographs can be very helpful in identifying dysmorphic features. Avoid using words like "abnormal" as these are value-laden words.]

Maria: Yes -- she definitely looked like something was different. My family always called it Down syndrome. But I've seen children with Down syndrome, and she didn't really look like that.

Doctor: It would be really helpful to actually see a picture, and to find out if any medical workup was ever done to determine why she had problems.

Maria: I can ask my aunt. We are going to see them at Thanksgiving, so I'll ask her then.

Doctor: What about your aunt's other 2 sons? Have they ever had any developmental or medical problems?

Maria: Oh, no, they are both in their 20s and doing really well. They went to college, and they haven't ever had any health problems that I know of. My aunt is ready for grandkids, but they aren't even married yet.

Tools

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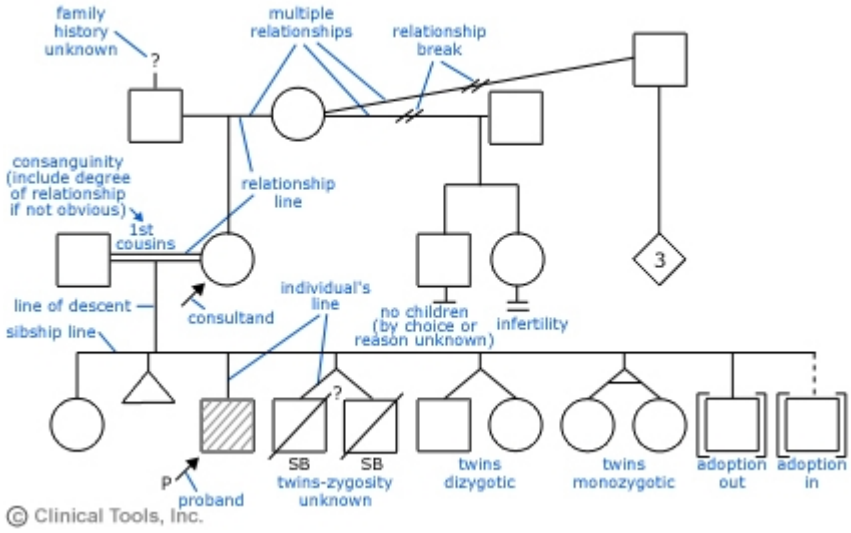

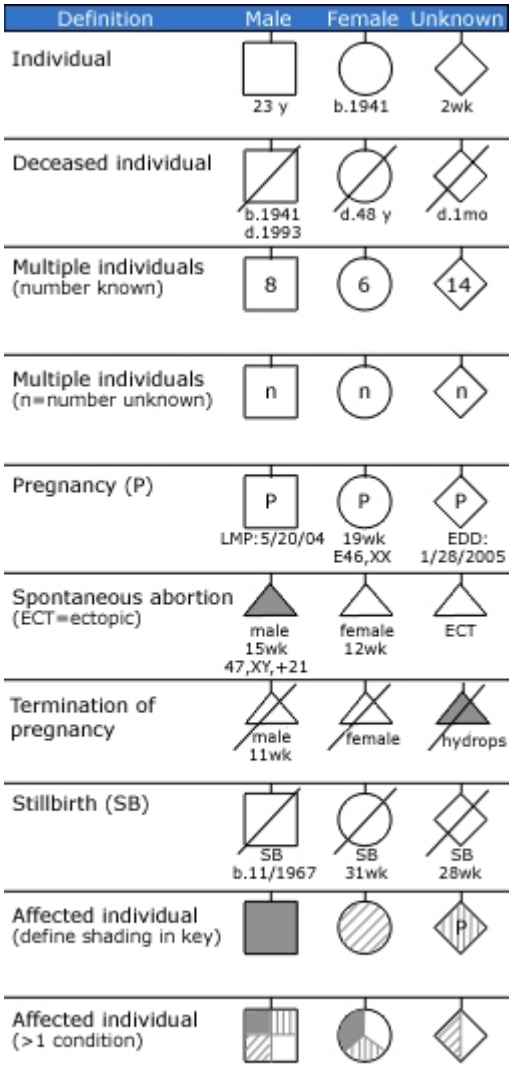

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FAMILY HISTORY OF BIRTH DEFECTS AND DEVELOPMENTAL DELAY

Questions to Ask

It is relatively common that patients do not have all of the information needed to adequately assess the family history when you first discuss it. In these cases, it may be helpful to provide patients with a list of questions in order to obtain necessary information from relatives.

It should also be noted that histories might not be reported accurately for a variety of reasons. For instance in Maria's case, if further family history was not taken, one might assume from her screening form that her cousin had Down syndrome. Mental retardation and a heart defect are consistent with Down syndrome, but they may also be found in combination with many other conditions. Family members may apply familiar diagnoses like Down syndrome to anyone with a mental retardation

syndrome. It is critical to confirm diagnoses so that correct recurrence risks and management options can be provided.

When There is a History of Congenital Anomalies

Ask these list of questions to ask when there is a family history of congenital anomalies.

For the child or adult with congenital anomalies or developmental variants:

- Has any explanation been identified or are specific diagnoses being considered?
- Has any testing or additional evaluation been done (chromosome studies, DNA-based testing, imaging, specialized exams, etc.)?
- Does the affected individual have any of the following:
    - anomalies in addition to those bringing the person to attention (include minor variants, anomalies of the hands and feet, short or disproportionate stature, etc.)?
    - small or large head size?
    - dysmorphic facial features such as unusual placement or appearance of the eyes, nose, mouth, and/or ears?
    - birthmarks? If so, document number, color, size, and shape.
    - vision, hearing, and/or speech deficits? If so, document deficit type, severity, and age of onset.
    - learning disabilities, behavioral problems, or difficulty in school?
    - delayed developmental milestones?
    - other medical problems (neurological, muscle weakness, feeding issues)?
- Does the affected individual resemble other family members in appearance?

For the parents of an affected individual:

- Did the mother
    - have any pregnancy complications (premature labor and/or delivery, placental problems, oligohydramnios, polyhydramnios, breech presentation/delivery, fetal distress, C-section)?
    - have any infections (syphilis, rubella, toxoplasmosis, cytomegalovirus, HIV, herpes simplex, unexplained rashes, etc.) or illnesses (diabetes, epilepsy, cardiovascular disease, PKU, myotonic dystrophy, etc.) during the pregnancy? If so, document diagnosis, treatment, and gestational timing.
    - take any medications during the pregnancy? If so, document the medication, dosage, and gestational timing.
    - use alcohol, tobacco products, or street drugs during the pregnancy? If so, document what was used, amount, and gestational timing.
    - have any prenatal testing (ultrasound, maternal serum screening, amniocentesis, etc.)?
- Are the parents of the affected individual blood relatives? If so, document the exact relationship.

For the remainder of the family:

- Have other babies been born with birth defects? If so, describe the anomalies and document any of the above information that is known.
- Does anyone else in the family have any of the following:

- mental retardation or learning disabilities?
- a history of pregnancy losses (miscarriages, stillbirths, neonatal deaths)?
- a neurological condition? If so, document the diagnosis if known, symptoms, and age of onset.
- muscle weakness? If so, document the diagnosis if known, symptoms, and age of onset.
- hearing or vision loss? If so, document the severity and age of onset.

(Adapted from Bennett 1999)

When There is a History of Mental Retardation

Ask these questions when there is a family history of mental retardation.

For the child or adult with mental retardation or developmental delay:

- Has any explanation been identified or are specific diagnoses being considered?
- Has any testing or additional evaluation been done (chromosome studies, DNA-based testing, metabolic studies, imaging, specialized exams, etc.)?
- What is the severity of the mental retardation (mild: 50-55 to 70; moderate: 35-40 to 50-55; severe: 20-25 to 35-40; profound: < 20-25)?
- At what age were the delays noted?
- Are the deficits static or progressive?
- Does the affected individual have
    - a history of early postnatal trauma (malnutrition, abuse, neglect)?
    - a history of severe childhood illness (recurrent infections, episodic vomiting, intermittent coma, hypoglycemia episodes, chronic diarrhea)?
    - congenital anomalies? If so, see "Questions to Ask When There Is a Family History of Congenital Anomalies."
    - a small or large head size?
    - dysmorphic features (unusual placement or appearance of the eyes, nose, mouth, and/or ears; sparse, patchy, brittle, kinky, or excessive hair)?
    - abnormal behaviors (self-injury, hand flapping, etc.)?
    - vision, hearing, and/or speech deficits? If so, document deficit type, severity, and age of onset.
    - unusual skin pigmentation? If so, describe color, pattern, size, shape, etc.
    - skeletal anomalies?
    - joint laxity?
    - unusual dietary habits?
    - unusual body odor (especially when ill)?
    - enlarged liver or spleen?
    - large testes?
    - neurological or neuromuscular abnormalities (seizures, weakness, hypotonia, hypertonia, abnormal gait, involuntary movements, etc.)?
- What are the heights of affected individual, parents, and siblings?

For the parents of an affected individual:

- Did the mother have any of the following:
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    - have any prenatal testing (ultrasound, maternal serum screening, amniocentesis, etc.)?
- What are the intellectual abilities of parents?
- Are the parents of the affected individual blood relatives? If so, document the exact relationship.

For the remainder of the family:

- Does anyone else in the family have any of the following:
    - mental retardation or learning disabilities?
    - pregnancy losses (miscarriages, stillbirths, or infant deaths)?
    - congenital anomalies?

(Adapted from Bennett 2010)

MARIA'S AUNT'S HISTORY

Pedigree Check

Click on the link to Maria's Aunt's History in the Related Resources section to review the family history as it currently stands and to compare it to your own version before proceeding.

Maria's Aunt's History

Doctor: And what about your father's other sister. How is her health?

Maria: She has been really healthy until recently. She just found out she has cancer. I think it is kidney cancer. Now that I think about it, my grandma might also have had kidney cancer.

FAMILY HISTORY OF KIDNEY CANCER

A Cancer Family History Typically Includes the Following

- Both maternal and paternal relatives. Hereditary cancer syndromes can be inherited from either the mother or the father.
- Notation of nonpaternity, consanguinity, and use of assisted reproductive technology (e.g., donor egg or sperm).

- Race, ancestry, and ethnicity information for all grandparents. This may influence decisions about genetic testing, because specific mutations (so-called founder mutations) may occur with increased frequency in selected populations.
- Seemingly unrelated conditions, such as birth defects or other nonmalignant conditions of children and adults, as they may aid in the diagnosis of a cancer susceptibility syndrome.
- A minimum of 3 generations

(Excerpted from NCI 2004a)

For Any Relative With Cancer, Collect the Following Information

- Type of each primary cancer
- Age of diagnosis for each primary cancer
- Where the relative was diagnosed and/or treated
- If the individual is still living, current age; if deceased, age at death and cause of death
- Carcinogenic exposures (e.g., tobacco use, radiation exposure)
- Other significant health problems

(Excerpted from NCI 2004a)

For Any Relative Not Affected With Cancer, Collect the Following Information

- Current age or age at death
- If deceased, cause of death
- Any surgeries that reduce the risk for cancer
- Whether routinely screened for cancer
- Any nonmalignant features of the syndrome in question
- Carcinogenic exposures
- Other significant health problems

(Excerpted from NCI 2004a)

ADDITIONAL CANCER HISTORY

Doctor: Kidney cancer is an unusual cancer that can sometimes run in families. Let me finish taking the family history, and we can talk more about this. Does your aunt have other medical problems?

Maria: Other than the cancer, she doesn't have any problems that I am aware of. I guess she had some blood in her urine and pain in her back that caused her to go to the doctor. She has 2 daughters and 2 sons. They are still pretty young, like between the ages of 8 and 15.

Doctor: How about your father's parents? You mentioned that your grandmother might also have had kidney cancer. Is she still living?

Maria: No, and I didn't really know her. She died before I was born. But I think she was about 60 when she passed away. I'm pretty sure it was kidney cancer. I think my dad was surprised when he found out about my aunt because it was the same kind as their mom. My grandfather is still alive. He has bad emphysema, though. He is 73.

Doctor: Does he smoke now, or did he ever smoke?

Maria: Oh yeah -- a couple packs a day for as long as I've known him.

Doctor: How about your aunt with the kidney cancer or your grandmother -- did they smoke?

Maria: My aunt has always been a heavy smoker. She drinks a lot, too. And I'm pretty sure my grandma smoked when she was alive. It seems like everyone did back then. I can ask my dad.

Doctor: Do you know if your father's sister or your grandmother worked outside the home?

Maria: My aunt has worked for several years as an administrator. I don't think my grandma ever worked other than raising her family.

Tools

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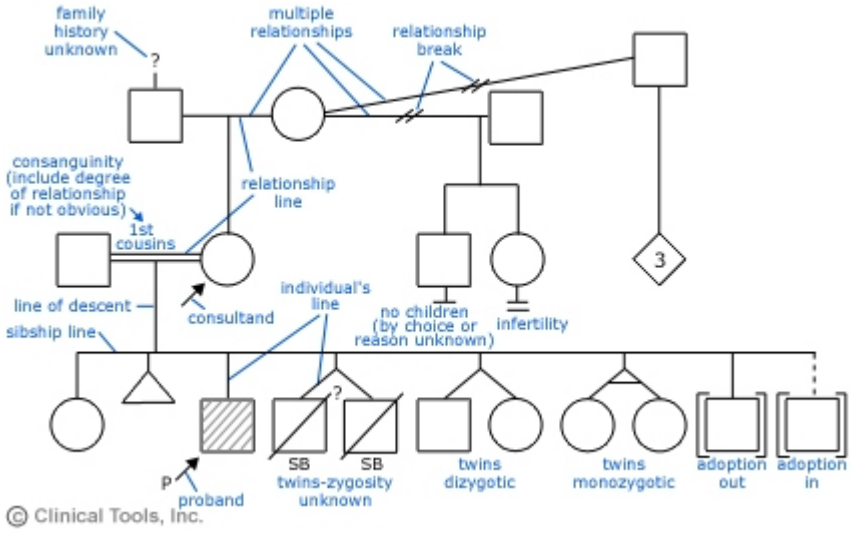

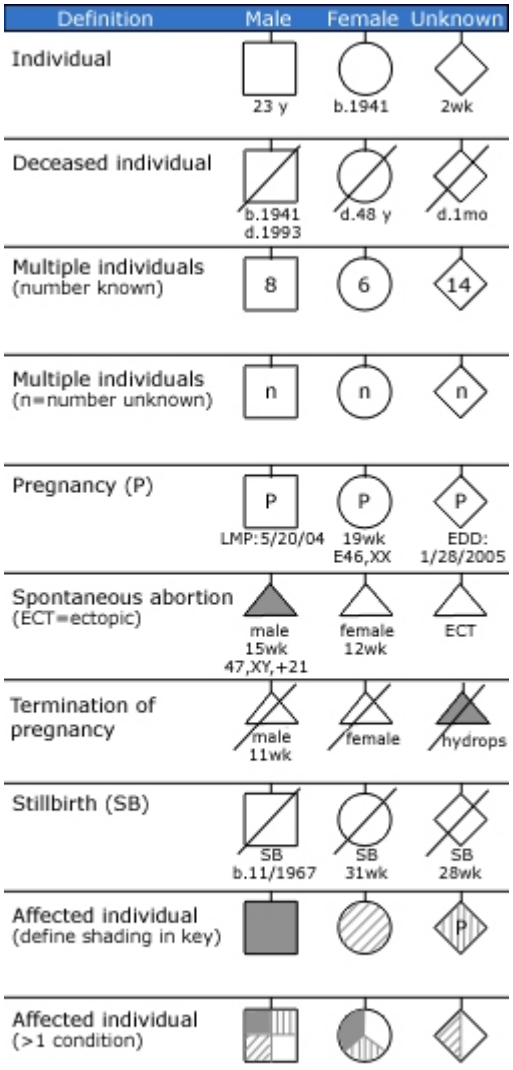

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MARIA'S MATERNAL FAMILY HISTORY

Pedigree Check

Maria's Maternal Family History

Doctor: Let's talk about your mother's family. How old is your mother and how is her health?

Maria: Oh, my mom is in great health. She wears me out! She is 50.

Doctor: How many brothers and sisters does she have?

Maria: She has 4 sisters, no brothers.

Doctor: Do they have the same mother and father?

Maria: Yes.

Doctor: What are your aunts' ages?

Maria: Let's see. I think the youngest is 45, then is my aunt Ruth who is 48, then my mom, then the older two, who are about 53 and 55.

Doctor: Do they have any significant health problems?

Maria: No, my mom's family is really active and healthy. All of my aunts had kids and they are fine.

Doctor: How about your grandparents -- how old are they?

Maria: Well, my grandfather died 2 years ago from prostate cancer. He had just turned 78. My grandma is 80. She is actually doing really well. I hope I'm that healthy when I'm her age.

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Any individual with the following:

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    - unexplained
    - progressive
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- Other unusual physical findings
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    - abnormal pigmentation (particularly if associated with other abnormal findings)
    - significant short stature
- A recognized single-gene (cystic fibrosis, muscular dystrophy) or chromosomal (Down syndrome, translocation) disorder

- Congenital or early-onset deafness or blindness
- Unexplained neuromuscular conditions, particularly with early onset (movement disorders, ataxia, hypotonia, seizures)
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    - loss of developmental milestones
    - unusual odors
- Reproductive abnormalities
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    - infertility: oligospermia or azoospermia, congenital absence of the vas deferens, premature ovarian failure
    - recurrent pregnancy loss (generally defined as 3 or more miscarriages or stillbirths)
- Common conditions
    - with an unusual presentation
        - an earlier age of onset than usual (colorectal cancer at 40 years, dementia at 50 years)
        - more severe course than usual
        - combined with other typically unrelated findings or dysmorphic features
        - multiple primary cancers in a single person
        - bilateral disease in paired organs
    - that appear to be "running in the family," particularly if suspicious for a single-gene pattern of inheritance (mental illness, diabetes)
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(Adapted from Bennett 2010)

Of course, the types of findings that are currently significant to your patient may vary depending on the presenting indication. For instance, a known or suspicious family history of cystic fibrosis will likely warrant more consideration for a patient who could become pregnant when compared to an individual in his or her 50s with no symptoms suggestive of respiratory or pancreatic disease. However, once you recognize a potential genetic risk, you do the family a great service in discussing potential implications and genetics referral, even if they are not immediate concerns for your patient.

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- Specifically inquire about cancers in the family

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Remember

- Confirm siblings share the same mother and father
- Remind family that you are interested in deceased relatives, too
- Define abbreviations in a legend
- Avoid leading questions ("So everyone is healthy?" vs. "Is everyone healthy?")
- Avoid value-laden terminology ("abnormal," "bad")
- Other questions may be appropriate based on indication (exposure history in preconception/prenatal counseling)

In Closing

- Does anyone else in your family have health problems or any unusual physical features that we haven't talked about?
- Is there anything that seems to run in your family?
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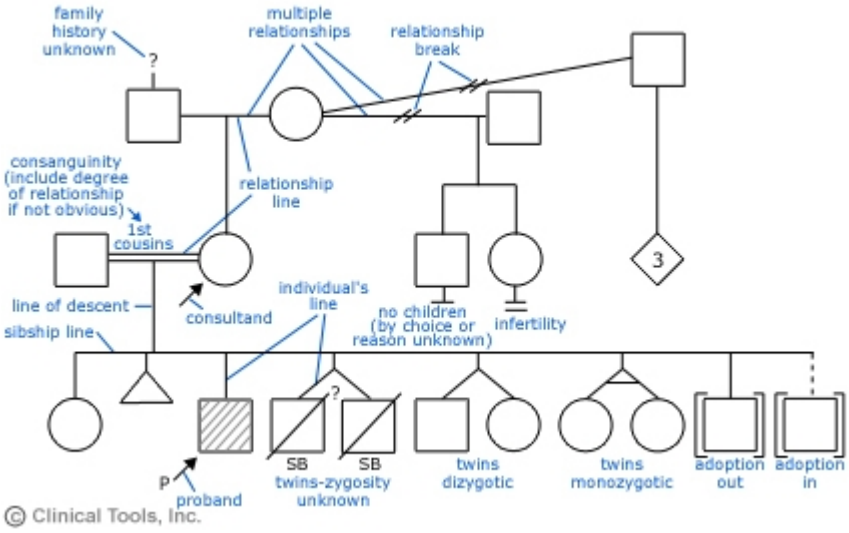

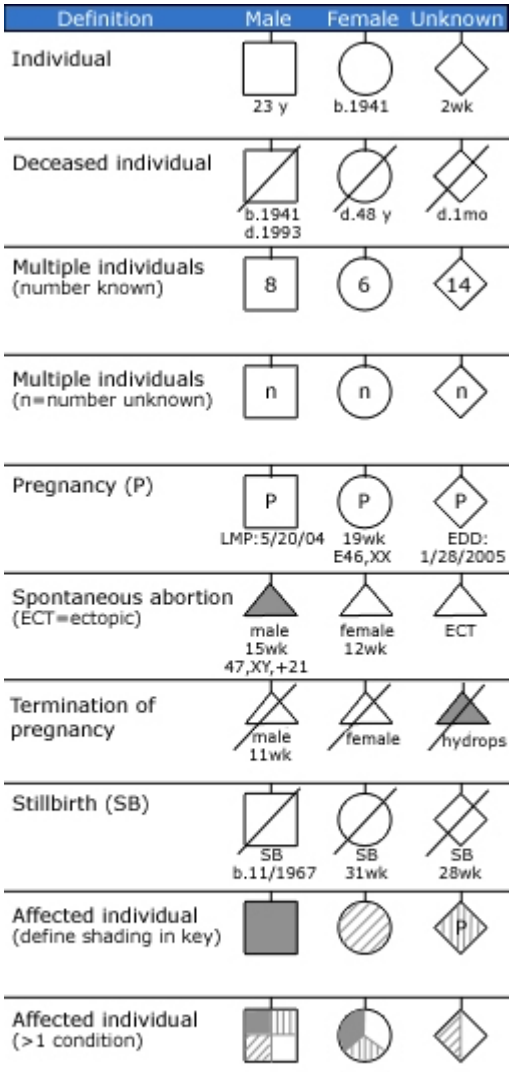

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MARIA'S HUSBAND'S FAMILY HISTORY

Pedigree Check

Maria's Husband's Family History

Doctor: Let's turn to your husband's family for a minute. He is 30 years old, right? How is his health?

Maria: Right. He just turned 30, and he is in perfect health.

Doctor: Does he have any brothers and sisters?

Maria: We don't know because he was adopted. I worry a lot because we don't know anything about what might run in his family.

Doctor: Do you know anything about his biological family? Like where they were from or why he was placed for adoption?

Maria: Not really. Just that his mom was about 21 when he was born and placed for adoption. We think his mom was from Mexico.

Doctor: Does Joe have any children from previous relationships?

Maria: [Laughs] No, not that I know of!

Tools

The following tools may be used throughout the case study to reference as needed.

Family History Red Flags

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The following are general red flags:

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(Adapted from Bennett 2010)

Of course, the types of findings that are currently significant to your patient may vary depending on the presenting indication. For instance, a known or suspicious family history of cystic fibrosis will likely warrant more consideration for a patient who could become pregnant when compared to an individual in his or her 50s with no symptoms suggestive of respiratory or pancreatic disease. However, once you recognize a potential genetic risk, you do the family a great service in discussing potential implications and genetics referral, even if they are not immediate concerns for your patient.

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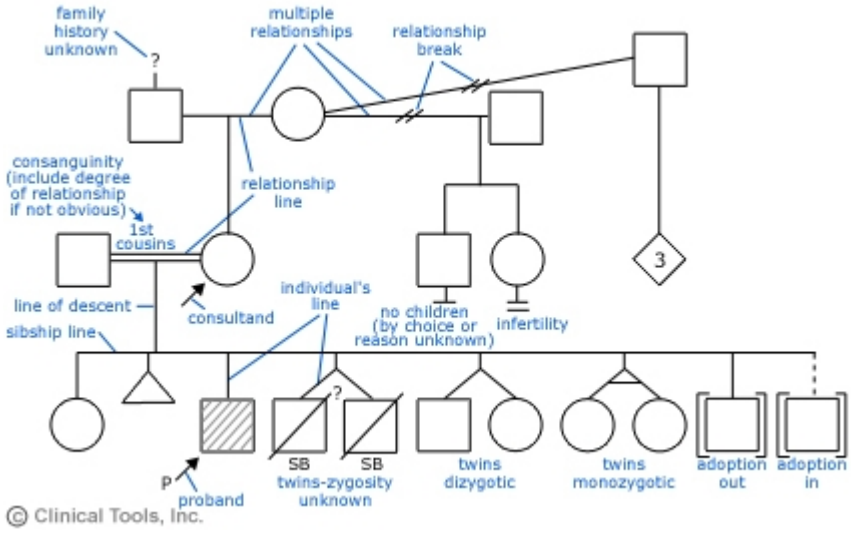

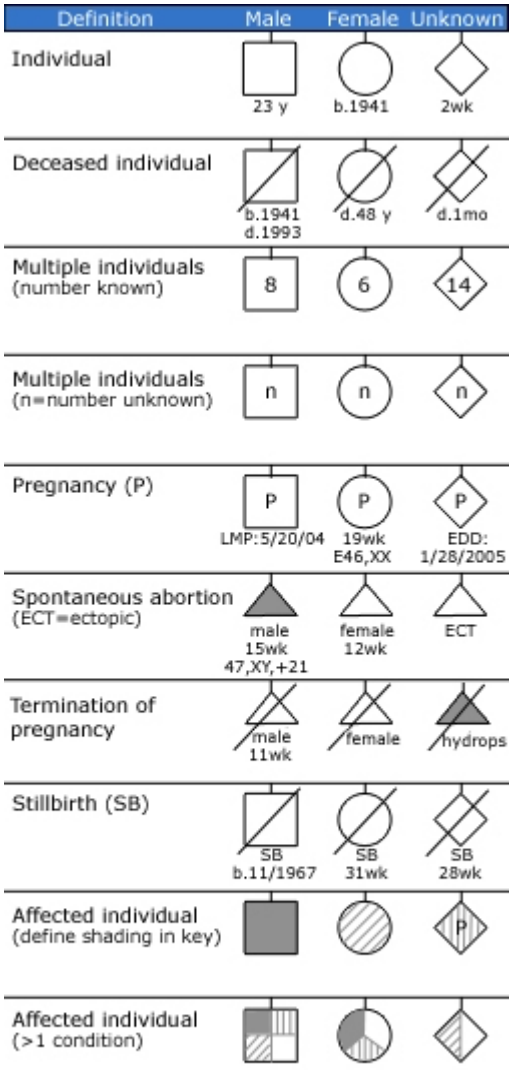

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WRAPPING UP THE FAMILY HISTORY

Summary of the Family History

Doctor: I'd like to ask you some more general questions about your family. Is there any other history of cancer in your family?

Maria: No, not that I know of, anyway.

Doctor: You mentioned your half brother and your cousin who died as infants and that the cousin had birth defects. Are you aware of any other relatives with birth defects or babies that didn't survive childhood?

Maria: No. I don't think there were any others.

Doctor: How about any history of learning disabilities or mental retardation?

Maria: No, just my cousin who apparently wasn't developing right. I don't think she ever could sit up very well or do other things that babies do.

Doctor: What is the country of origin of your ancestors? For example, are they French, Spanish, African-American?

Maria: Hmm. My mom always says she is "Heinz 57." My dad's father emigrated from Mexico and his mother was African-American.

Doctor: Do you know more about your mother's family? Are they Caucasian, black?

Maria: I think my mom's relatives are mostly white. Is that important?

Doctor: Some inherited conditions are more common in certain ethnic groups. It can help us identify problems that may run in a family and may make a difference in the approach we use to any genetic blood tests. Some problems also occur more often in the children of couples who are related, such as cousins. Are you and your husband related as cousins, or were your parents or grandparents cousins

Maria: [Laughs nervously] No, not that I know of.

Doctor: Is there anything else you think it is important for me to know about your family? [This gives clients an opportunity to bring up anything you haven't. Sometimes clients leave the most concerning issues until last, as they may be afraid or embarrassed to bring them up.]

Maria: No, I think that pretty much covers everything.

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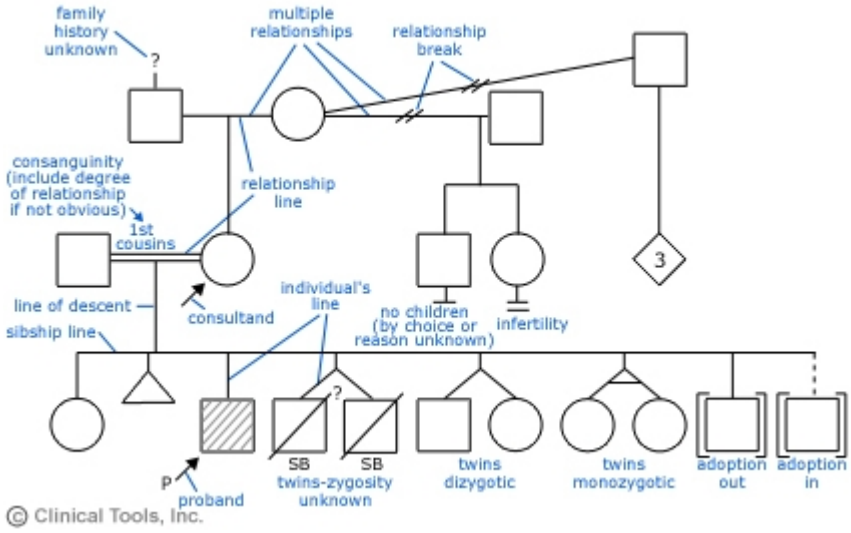

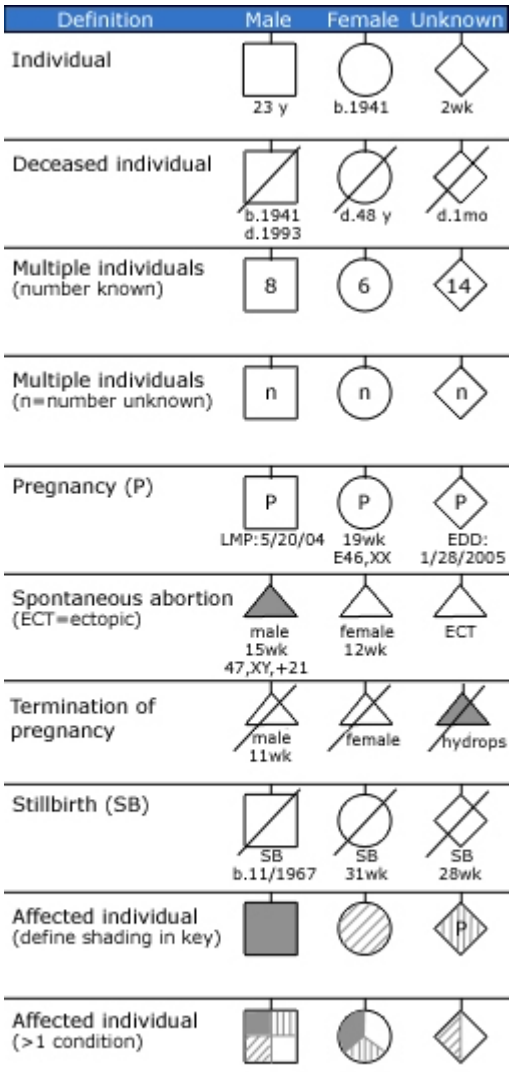

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ASSESS THE CANCER FAMILY HISTORY

Assess the Cancer Family History

Review the final family history in the Related Resources section.

What Do You Do With This Family History Information?

Let's start with the family history of kidney cancer. Assuming that the history Maria provided is correct (this should be confirmed through medical records and/or death certificates), she has 2 biologically related relatives with kidney cancer. One of these relatives certainly had an earlier age of onset than is typical. The family history of kidney cancer may be due to inherited factors. Having 2 affected family members could also be the result of shared environmental exposures (both are reported smokers -- a known risk factor) or chance alone.

CALCULATE MARIA'S MAXIMAL RISK

View the family pedigree
Before taking the quiz to follow, review Maria's family history.

CALCULATE MARIA'S RISK

An autosomal dominant cancer syndrome is possible, based on the family history, and would represent the greatest risk to Maria. If Maria's aunt (and grandmother, by presumption) were found to have an autosomal dominant cancer syndrome, such as Von Hippel-Lindau, what would be the likelihood that Maria also inherited the gene mutation?

1. 0%
    - Feedback:

      Incorrect. The risk is one-fourth or 25%, calculated as: 1/2 (chance that Maria's father inherited the gene mutation from his mother) x 1/2 (chance that Maria inherited the gene mutation if her father has it) = 1/4. However, it should be noted that Maria's father is 50 years old and reportedly has no personal history of cancer. To further refine the risk, a more complex calculation (Bayesian analysis) can be used to incorporate the likelihood that he would be cancer-free based on his age.
2. 5%
    - Feedback:

      Incorrect. The risk is one-fourth or 25%, calculated as: 1/2 (chance that Maria's father inherited the gene mutation from his mother) x 1/2 (chance that Maria inherited the gene mutation if her father has it) = 1/4. However, it should be noted that Maria's father is 50 years old and reportedly has no personal history of cancer. To further refine the risk, a more complex calculation (Bayesian analysis) can be used to incorporate the likelihood that he would be cancer-free based on his age.
3. 25%
    - Feedback:

      Correct. The risk is one-fourth or 25%, calculated as: 1/2 (chance that Maria's father inherited the gene mutation from his mother) x 1/2 (chance that Maria inherited the gene mutation if her father has it) = 1/4. However, it should be noted that Maria's father is 50 years old and reportedly has no personal history of cancer. To further refine the risk, a more complex calculation (Bayesian analysis) can be used to incorporate the likelihood that he would be cancer-free based on his age.
4. 50%
    - Feedback:

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personal history of cancer. To further refine the risk, a more complex calculation (Bayesian analysis) can be used to incorporate the likelihood that he would be cancer-free based on his age.

To investigate if there is indeed a familial chromosome abnormality that explains this constellation of family history findings, what would be the next best course of action?

1. Order blood chromosome studies on Maria.
    - Feedback:

      This is NOT the best choice. Maria's sister-in-law should be offered blood chromosome analysis, due to her personal history of recurrent pregnancy loss. However, as a nonbiological relative, her results would not assist in determining if Maria's family history of reproductive losses were due to a familial chromosome abnormality.
2. Offer prenatal diagnosis for fetal chromosome analysis when Maria becomes pregnant.
    - Feedback:

      This is NOT the best choice. Maria's sister-in-law should be offered blood chromosome analysis, due to her personal history of recurrent pregnancy loss. However, as a nonbiological relative, her results would not assist in determining if Maria's family history of reproductive losses were due to a familial chromosome abnormality.
3. Offer blood chromosome analysis to Maria's father.
    - Feedback:

      This is the best choice. It is always best to first perform any type of genetic testing on someone who is affected or who is most closely related to an affected individual. Because Maria's father is the biological link to all of those experiencing pregnancy loss or infant death, he is the ideal starting point for further testing. However, if he is unable or unwilling, other family members, such as Maria's brother, may be suitable. (Maria's brother should be offered blood chromosome analysis simply based on the history of recurrent loss, as should his wife.)
4. Offer blood chromosome analysis to Maria's sister-in-law, who has experienced recurrent pregnancy loss.
    - Feedback:

      This is NOT the best choice. Maria's sister-in-law should be offered blood chromosome analysis, due to her personal history of recurrent pregnancy loss. However, as a nonbiological relative, her results would not assist in determining if Maria's family history of reproductive losses were due to a familial chromosome abnormality.

Now, let's consider the family history of recurrent pregnancy loss, infant death, and congenital anomalies. Since all of these findings can be etiologically related, we will first look at the pedigree in this way.

First, are all of the individuals who experienced pregnancy loss and infant deaths biologically related to each other?

1. Yes
    - Correct
2. No

- Incorrect

If the history of kidney cancer is due to clearly genetic factors, which of the following forms of inheritance would be most likely based on the family history? You can use the checklist of pedigree clues for these forms of inheritance to assess the pedigree.

Autosomal Dominant

- Affected fathers can have affected sons or daughters.
- Affected mothers can have affected sons or daughters.
- Condition appears in multiple successive generations.
- Males and females are both affected, usually in equal proportions.
- Unaffected individuals do not have affected children (exceptions occur due to de novo mutations, variable expressivity, reduced penetrance or sex-limited expression).

Autosomal Recessive

- Unaffected parents have affected children.
- Condition usually appears in a single group of siblings.
- Males and females are both affected, usually in equal proportions.
- Conditions are more common when there is consanguinity.

X-Linked Recessive

- Males are exclusively or much more commonly affected than females.
- Affected males are related to each other through unaffected females (carriers).
- Children of affected fathers are all unaffected.
- Unaffected fathers do not transmit the condition to any of their descendants.

X-Linked Dominant

- Males and females may be affected.
- Affected males are typically more severely affected than affected females.
- Affected males transmit the condition to none of their sons and all of their daughters.
- Affected females can have affected daughters or sons.

Mitochondrial

- Males and females are both affected, usually in equal proportions.
- Only females transmit the condition to their children.
- Affected individuals are related to each other through females.
- Condition appears in multiple generations.

Chromosomal

    - Best identified by cytogenetic testing when any of the following clinical findings are present:
- Combinations of major and/or minor congenital anomalies.
- Mental retardation with or without major/minor anomalies.
- Recurrent pregnancy loss.
- Sexual development disorders.
- Infertility.
- Stillbirth or infant death.

1. Autosomal dominant
    - Feedback:

      This is the best answer. Kidney cancer appears in multiple successive generations, which is the hallmark of autosomal dominant inheritance. In addition, most hereditary cancer syndromes are inherited in an autosomal dominant manner.
2. Autosomal recessive
    - Feedback:

      The best answer is autosomal dominant. Kidney cancer affects 2 females in the family. Therefore, the condition is not exclusively or much more commonly seen in males, as is the primary feature of X-linked recessive inheritance.
3. X-linked recessive
    - Feedback:

      The best answer is autosomal dominant. Kidney cancer appears in multiple successive generations, which is the hallmark of autosomal dominant inheritance. In addition, most hereditary cancer syndromes are inherited in an autosomal dominant manner.
4. X-linked dominant
    - Feedback:

      The best answer is autosomal dominant. Kidney cancer appears in multiple successive generations, which is the hallmark of autosomal dominant inheritance. In addition, most hereditary cancer syndromes are inherited in an autosomal dominant manner.
5. Mitochondrial
    - Feedback:

      The best answer is autosomal dominant. Kidney cancer appears in multiple successive generations, which is the hallmark of autosomal dominant inheritance. In addition, most hereditary cancer syndromes are inherited in an autosomal dominant manner.
6. Chromosomal
    - Feedback:

      The best answer is autosomal dominant. Kidney cancer appears in multiple successive generations, which is the hallmark of autosomal dominant inheritance. In addition, most hereditary cancer syndromes are inherited in an autosomal dominant manner.

Since all of these individuals are biologically related, a common etiology would likely represent the greatest risk for Maria's children. Is there a form of inheritance that is consistent with this pedigree? You can use the checklist of pedigree clues for these forms of inheritance to assess the pedigree.

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- Condition appears in multiple successive generations.
- Males and females are both affected, usually in equal proportions.
- Unaffected individuals do not have affected children (exceptions occur due to de novo mutations, variable expressivity, reduced penetrance or sex-limited expression).

Autosomal Recessive

- Unaffected parents have affected children.
- Condition usually appears in a single group of siblings.
- Males and females are both affected, usually in equal proportions.
- Conditions are more common when there is consanguinity.

X-Linked Recessive

- Males are exclusively or much more commonly affected than females.
- Affected males are related to each other through unaffected females (carriers).
- Children of affected fathers are all unaffected.
- Unaffected fathers do not transmit the condition to any of their descendants.

X-Linked Dominant

- Males and females may be affected.
- Affected males are typically more severely affected than affected females.
- Affected males transmit the condition to none of their sons and all of their daughters.
- Affected females can have affected daughters or sons.

Mitochondrial

- Males and females are both affected, usually in equal proportions.
- Only females transmit the condition to their children.
- Affected individuals are related to each other through females.
- Condition appears in multiple generations.

Chromosomal

    - Best identified by cytogenetic testing when any of the following clinical findings are present:
- Combinations of major and/or minor congenital anomalies.
- Mental retardation with or without major/minor anomalies.
- Recurrent pregnancy loss.
- Sexual development disorders.
- Infertility.
- Stillbirth or infant death.

1. Autosomal dominant
    - Feedback:

      This is NOT the best answer. Chromosomal is the most likely mode of inheritance if all of these findings are related to each other. Balanced structural chromosome abnormalities can segregate at meiosis to create a variety of unbalanced gametes (with deletions or duplications of genetic material). These imbalances can lead to recurrent pregnancy loss, stillbirth or infant death, developmental delay/mental retardation, and/or congenital anomalies. It is possible that Maria's brother, father, paternal aunt, and possibly a paternal grandparent could all have a balanced chromosomal rearrangement that leads to greater risk for abnormal reproductive outcomes.

2. Autosomal recessive
    - Feedback:

      This is NOT the best answer. Chromosomal is the most likely mode of inheritance if all of these findings are related to each other. Balanced structural chromosome abnormalities can segregate at meiosis to create a variety of unbalanced gametes (with deletions or duplications of genetic material). These imbalances can lead to recurrent pregnancy loss, stillbirth or infant death, developmental delay/mental retardation, and/or congenital anomalies. It is possible that Maria's brother, father, paternal aunt, and possibly a paternal grandparent could all have a balanced chromosomal rearrangement that leads to greater risk for abnormal reproductive outcomes.
3. X-linked recessive
    - Feedback:

      This is NOT the best answer. Chromosomal is the most likely mode of inheritance if all of these findings are related to each other. Balanced structural chromosome abnormalities can segregate at meiosis to create a variety of unbalanced gametes (with deletions or duplications of genetic material). These imbalances can lead to recurrent pregnancy loss, stillbirth or infant death, developmental delay/mental retardation, and/or congenital anomalies. It is possible that Maria's brother, father, paternal aunt, and possibly a paternal grandparent could all have a balanced chromosomal rearrangement that leads to greater risk for abnormal reproductive outcomes.
4. X-linked dominant
    - Feedback:

      This is NOT the best answer. Chromosomal is the most likely mode of inheritance if all of these findings are related to each other. Balanced structural chromosome abnormalities can segregate at meiosis to create a variety of unbalanced gametes (with deletions or duplications of genetic material). These imbalances can lead to recurrent pregnancy loss, stillbirth or infant death, developmental delay/mental retardation, and/or congenital anomalies. It is possible that Maria's brother, father, paternal aunt, and possibly a paternal grandparent could all have a balanced chromosomal rearrangement that leads to greater risk for abnormal reproductive outcomes.
5. Mitochondrial
    - Feedback:

      This is NOTthe best answer. Chromosomal is the most likely mode of inheritance if all of these findings are related to each other. Balanced structural chromosome abnormalities can segregate at meiosis to create a variety of unbalanced gametes (with deletions or duplications of genetic material). These imbalances can lead to recurrent pregnancy loss, stillbirth or infant death, developmental delay/mental retardation, and/or congenital anomalies. It is possible that Maria's brother, father, paternal aunt, and possibly a paternal grandparent could all have a balanced

chromosomal rearrangement that leads to greater risk for abnormal reproductive outcomes.

6. Chromosomal
    - **Feedback:**
      This is the best answer. Chromosomal is the most likely mode of inheritance if all of these findings are related to each other. Balanced structural chromosome abnormalities can segregate at meiosis to create a variety of unbalanced gametes (with deletions or duplications of genetic material). These imbalances can lead to recurrent pregnancy loss, stillbirth or infant death, developmental delay/mental retardation, and/or congenital anomalies. It is possible that Maria's brother, father, paternal aunt, and possibly a paternal grandparent could all have a balanced chromosomal rearrangement that leads to greater risk for abnormal reproductive outcomes.

FOLLOW-UP

Follow-Up

After reviewing the family history, you decided to refer Maria to a genetic counselor at your local perinatal center. In the meantime, Maria's brother and sister-in-law had blood chromosome studies (karyotypes) as part of their evaluation for recurrent pregnancy loss. Maria's brother was found to be a carrier of a balanced translocation. Maria then had chromosome studies and was fortunately negative for the familial translocation.

The genetic counselor suspects that Maria's father, aunt, and possibly other family members also carry a balanced translocation. Maria's father has declined testing, feeling that the information will not impact his management. Maria's aunts, however, do plan to pursue chromosome studies -- mostly to help their children decide if they should be tested.

Because Maria was most concerned about this aspect of the family history, you both agreed that she would meet with a reproductive genetic counselor first. However, you also forwarded her pedigree to a hereditary cancer program to review. Cancer genetic counselors there felt that Maria was a good candidate for a cancer genetics referral. Maria will be seen by their program in the next 6 months.

How to Locate Genetics Professionals

Review the Related Resources section for a list of organizations which maintain searchable databases of genetic counselors, physician geneticists, and other genetics professionals.

SUMMARY AND KEY POINTS

Summary and Key Points

As our understanding of the genetic contribution to disease continues to improve, our medical family histories will play an increasing role in determining appropriate management strategies.

- All healthcare providers should be assessing the family histories of their patients.

- Screening forms are acceptable tools, but care should be taken to choose those that adequately elicit family history information and address your patient's concerns.

The pedigree is the most expeditious, concise, accurate, and visually obvious representation of a family's relationships and medical history.

- Standards exist for pedigree symbols and nomenclature to ensure that pedigrees are easily interpreted by others (Bennett et al. 1995).
- The **most important step** in taking a family history is recognizing findings that indicate a potential genetic etiology. Once identified, the history should be evaluated by the provider or the provider should make a genetics referral.

Individuals with **findings that are uncommon** or who have **unusual presentations of common disorders** should cause you to consider a genetic etiology and referral. Some examples of red flags in the medical family history are shown below.

The following are general examples of red flags:

- Multiple family members with the same or related condition
- Familial "clustering" of cancers that may have the same etiology (cancer and endometrial cancer due to HNPCC mutation)
- Ethnicity known to be associated with increased risk for specific genetic conditions (sickle cell among those of African descent, BRCA mutations more common in Ashkenazi Jewish individuals)
- Consanguinity

Any individual with the following:

- Birth defects
- Mental retardation/developmental delay
- Other unusual physical findings (dysmorphic features, abnormal pigmentation, significant short stature)
- A recognized classic single-gene (cystic fibrosis, muscular dystrophy) or chromosomal (Down syndrome, translocation) disorder
- Congenital or early-onset deafness or blindness
- Unexplained neuromuscular conditions, particularly with early onset (movement disorders, ataxia, hypotonia, seizures)
- Symptoms suspicious for metabolic disease (failure to thrive, loss of milestones, unusual odors)
- Reproductive abnormalities (recurrent pregnancy loss, abnormal development, infertility)
- Common conditions with an unusual presentation (earlier onset or increased severity, combined with other unusual findings)
- Rare cancers/tumors
- Sudden premature death in an apparently healthy person

(Adapted from Bennett 1999, Table 3.1)

- Once the pedigree is assembled, it can be easily used to assess inheritance patterns and basic recurrence risks. (See pedigree clues and inheritance pattern fact sheet links at the right.)

- Some common mistakes to avoid in taking a family history are summarized below.
- Not taking a full 3-generation family history (patient, siblings, parents, aunts, uncles, grandparents) and more extended family history where indicated
- Assessing only the female's family history during the preconception or pregnancy visit
- Undisclosed nonpaternity, adoption, consanguinity, or assisted reproduction relationships may confuse pedigree interpretation
- Patients may know limited family history information or do not fully disclose it (i.e., belief that it is not relevant, feelings of guilt or embarrassment, fear of compromised privacy)
- Assuming that if only one person in a family has a condition, it is not genetic (e.g., could be due to a de novo mutation, reduced penetrance of the condition, small family size, variable expressivity in symptoms, or age of onset, etc.)
- Overlooking deceased individuals and pregnancy losses
- Making assumptions about ethnic background based on appearance or failing to take ethnicity into account altogether
- Failing to confirm diagnoses or abnormal findings before proceeding with genetic testing or altered management strategies (e.g., "Down syndrome" may be used by some patients as a general term to describe any individual with mental retardation)

For Your Practice

You may want to print or bookmark some of the following tools for use in your practice:

Tools

The following tools may be used throughout the case study to reference as needed.

Family History Red Flags

Individuals with findings that are uncommon or who have unusual presentations of common disorders should cause you to consider a genetic etiology and referral. Some examples of red flags in the medical family history are shown below.

The following are general red flags:

- Multiple family members with the same condition
- Familial "clustering" of cancers that may have the same etiology (colorectal cancer and endometrial cancer due to HNPCC mutation)
- Ethnicity known to be associated with increased risk for specific genetic conditions (sickle cell among those of African descent, BRCA mutations more common in Ashkenazi Jewish individuals)
- Consanguinity

Any individual with the following:

- Birth defects
    - isolated major congenital anomalies (cleft lip, congenital cardiac defects)
    - combinations of major and/or minor anomalies (extra digits, widely spaced eyes)
        - 2 or more major anomalies
        - 3 or more minor anomalies
        - 1 major and 2 minor anomalies
- Mental retardation/developmental delay, especially if

        - unexplained
        - progressive
        - associated with dysmorphic features, physical anomalies, or unusual medical conditions
- Other unusual physical findings
    - dysmorphic features
    - abnormal pigmentation (particularly if associated with other abnormal findings)
    - significant short stature
- A recognized single-gene (cystic fibrosis, muscular dystrophy) or chromosomal (Down syndrome, translocation) disorder
- Congenital or early-onset deafness or blindness
- Unexplained neuromuscular conditions, particularly with early onset (movement disorders, ataxia, hypotonia, seizures)
- Symptoms suspicious for metabolic disease
    - neonatal deaths/SIDS
    - failure to thrive
    - loss of developmental milestones
    - unusual odors
- Reproductive abnormalities
    - abnormal development: ambiguous genitalia, primary amenorrhea, hypogonadism
    - infertility: oligospermia or azoospermia, congenital absence of the vas deferens, premature ovarian failure
    - recurrent pregnancy loss (generally defined as 3 or more miscarriages or stillbirths)
- Common conditions
    - with an unusual presentation
        - an earlier age of onset than usual (colorectal cancer at 40 years, dementia at 50 years)
        - more severe course than usual
        - combined with other typically unrelated findings or dysmorphic features
        - multiple primary cancers in a single person
        - bilateral disease in paired organs
    - that appear to be "running in the family," particularly if suspicious for a single-gene pattern of inheritance (mental illness, diabetes)
- Rare cancers/tumors
- Sudden premature death in an apparently healthy person

(Adapted from Bennett 2010)

Of course, the types of findings that are currently significant to your patient may vary depending on the presenting indication. For instance, a known or suspicious family history of cystic fibrosis will likely warrant more consideration for a patient who could become pregnant when compared to an individual in his or her 50s with no symptoms suggestive of respiratory or pancreatic disease. However, once you recognize a potential genetic risk, you do the family a great service in discussing potential implications and genetics referral, even if they are not immediate concerns for your patient.

Pedigree Components

Major Components

- Consultant: person requesting services or asking questions
- Historian(s): person(s) providing the family history
- Recorder: person recording the family history
- Date the pedigree was taken or updated
- Minimum of 3 generations of family members; may be more based on indication or identified red flags (children, parents, siblings, grandparents, aunts/uncles, cousins)
- Age and birth date (or year) for all individuals
- Names (or initials when privacy is an issue) for easy reference, medical records request, etc. for all individuals
- Ethnic background for each of the 4 grandparents ("Do you know what country your ancestors originally came from?")
- Consanguinity ("Has anyone in your family had children with a biological or blood relative?"): record "denied" or show on pedigree with relationship if not implicit
- Exposure history when indicated (preconception/prenatal, personal or family history of cancer or other disease): occupation, medications, recreational drug and alcohol use, etc.
- Specifically ask if anyone in the family has had a child with a birth defect, mental retardation, or known genetic condition
- Specifically inquire about miscarriages, stillbirths, and neonatal deaths
- Specifically inquire about cancers in the family

Specific Circumstances

- **Significant medical history:** appropriately shade symbol and define in key; record age at diagnosis and relevant medical information (see targeted question lists by indication)
- **Ongoing pregnancies:** record gestational age, LMP, and/or EDC
- **Pregnancy losses:** use appropriate symbol and note gestational age, any etiology information, and if SAb (miscarriage), SB (stillbirth), TOP (termination), or ECT (ectopic)
- **Reproductive age individuals without children:** inquire if by choice or infertility
- **Deceased individuals:** age at death and cause of death
- **Healthy people with no findings of medical significance:** specifically note "A&W" (alive and well)
- **Unclear or uncertain family medical information (hearsay, family myths):** place information in quotes without assuming meaning or interpreting the actual medical facts yourself
- **Unknown or unavailable history:** place a "?" above their symbol

Remember

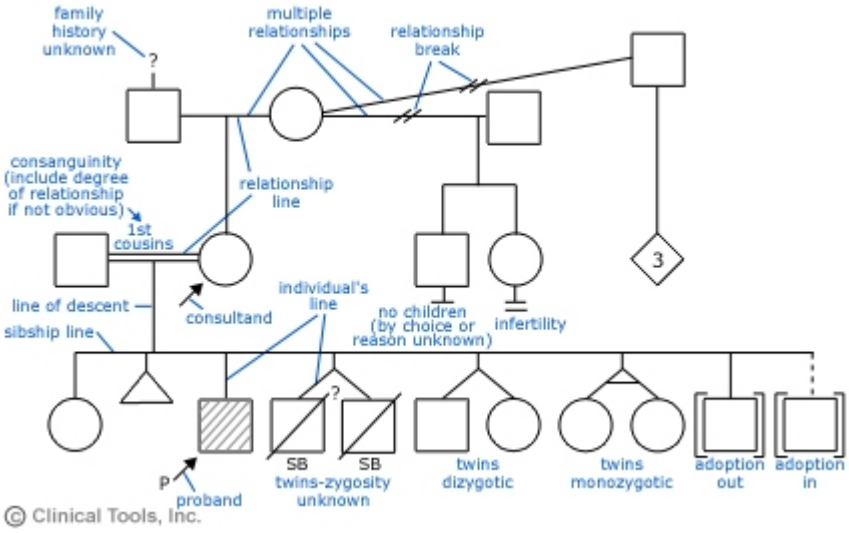
- Confirm siblings share the same mother and father
- Remind family that you are interested in deceased relatives, too
- Define abbreviations in a legend
- Avoid leading questions ("So everyone is healthy?" vs. "Is everyone healthy?")
- Avoid value-laden terminology ("abnormal," "bad")
- Other questions may be appropriate based on indication (exposure history in preconception/prenatal counseling)

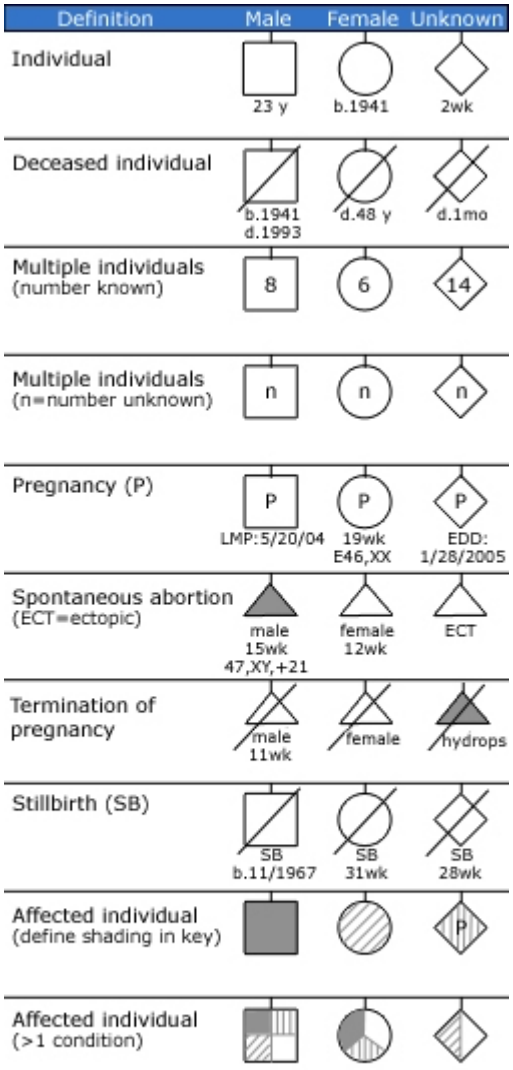
In Closing

- Does anyone else in your family have health problems or any unusual physical features that we haven't talked about?
- Is there anything that seems to run in your family?
- Is there anything else that you are concerned about that we haven't discussed?
- Is there anything else that you think is important for me to know?

(Adapted from Bennett 2010)

Pedigree symbols





Adapted from Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. /Am J Hum Genet./ 1995;56:745-52.

RESOURCES AVAILABLE THROUGH THIS MODULE:

- AAFP Core Educational Guidelines in Medical Genetics Edit
  A list endorsed by the American Academy of Family Physicians to provide a list of core educational guidelines for family practice residents.
- Adolescent/adult family history questionnaireEdit
  This is a comprehensive, paper-based screening form that includes past medical history, current exposures, reproductive history for females, and extended family history for a lengthy list of potentially inherited conditions, as well as a place for office notes regarding significant findings and plans.
- APHMG - Association of Professors of Human and Medical GeneticsEdit
  The website for the Association of Professors of Human and Medical Genetics.
- Cancer Family History Red FlagsEdit

Lists of family history red flags or findings that should prompt investigation or genetics referral.

- Cancer Genetics Services Directory - SearchEdit
  A database of professionals who provide cancer genetics services, including counseling and testing, from the National Cancer Institute. The database is searchable by type of cancer, family cancer syndrome, location, or name.
- Congenital AnomaliesEdit
  Questions to Ask When There Is a Family History of Congenital Anomalies
- Consanguinity Fact Sheet -- Debunking Common MythsEdit
  An article by Robin Bennett, MS, CGC debunking common myths of consanguinity.
- Final Family HistoryEdit
  Maria's final family history pedigree chart.
- GeneTestsEdit
  The GeneTests website offers an outstanding series of expert-authored GeneReviews that provide important information for clinicians to know about diagnosis, natural history, and genetic testing for genetic conditions. GeneTests.org also maintains databases of genetic testing laboratories and medical genetics clinics. There is no cost to use this website.
- Genetics Pedigree FormEdit
  Genetics Pedigree Form
- Infant/child family history questionnaireEdit
  This is a comprehensive, paper-based screening form that includes a child's past medical history, pregnancy and birth history, and maternal and paternal family histories for a lengthy list of potentially inherited conditions, as well as a place for office notes regarding significant findings and plans.
- Maria's Aunt's HistoryEdit
  A pedigree image of for reviewing Maria's family history.
- Maria's Final PedigreeEdit
- Maria's Husband's Family HistoryEdit
  An image of Maria's husband's family history.
- Maria's Mother's Family HistoryEdit
  Click on the pedigree image to review the family history on Maria's mother's side as it currently stands and to compare it to your own version before proceeding.
- Maria's PedigreeEdit
  A pedigree image to review the family history as it currently stands.
- Medical Family History Red FlagsEdit
  A list of family history red flags
- Medical history: Compiling your medical family treeEdit
  This Web page, from the Mayo Clinic, provides guidance for patients about what to include in a family history, basic pedigree construction (not consistent with Bennett et al., 1995), limitations of the family history, and how to approach family members. It also includes a very basic form with columns for "blood relative" and "health conditions."
- Mental RetardationEdit
  A list of probing questions for positive histories of mental retardation.

- My Family Health PortraitEdit
  This program, from the US Surgeon General's Family History Initiative, enables people to answer a series of questions about the number, relationship, and medical histories of their family members. This information is then used to generate a pedigree that the patient can bring to his or her physician for review. The program is relatively simplistic (does not distinguish half siblings from full siblings, includes a limited number of relatives, no risk assessment, etc.), but the Surgeon General's office plans to continue developing the tool. It is simple for the patient to complete, requires only about 10 to 15 minutes (if all of the health information is readily available), and the information is kept on one's own computer, minimizing security concerns.
- Pedigree CluesEdit
  Pedigree Clues
- Pedigree Clues - listEdit
  A list of pedigree clues for autosomal dominant, x-linked recessive, mitochondrial, autosomal recessive, x-linked dominant, and chromosomal traits.
- Pedigree symbolsEdit
  Reference guide
- Preconception / prenatal family history questionnaireEdit
  This is a comprehensive, paper-based screening form from the March of Dimes that includes past medical history, exposures history, reproductive history, and extended family history for a lengthy list of potentially inherited conditions, as well as a place for office notes regarding significant findings and plans.
- Recurrent Pregnancy LossEdit
  Questions to ask when there is a family history of recurrent pregnancy loss.
- Your Family History - Your FutureEdit
  From the National Society of Genetic Counselors, this Web page contains good general information for patients about what demographic and medical information to include in a medical family history, as well as basic instruction on how to assemble this information in pedigree form. The instructions are also available in a print-friendly PDF format that could be provided to patients.

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