# Genetics in Primary Care (GPC) Training Program Curriculum Materials

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Revised and updated, September, 2001

Genetics in Primary Care (GPC): A Faculty Development Initiative

# GPC Curriculum Materials

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Acknowledgements

# Acknowledgments

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Even with the terrific teamwork and contributions from these GPC members, we take responsibility for the content that remains. We look forward to learning more from this next phase of piloting the curriculum.

With regards,

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# Introduction to the GPC Curriculum

The materials in this notebook are designed to serve as a bridge between genetics and primary care. They are not intended as a freestanding curriculum: each module cites web-sites for additional background information and articles from the medical literature, including relevant consensus and policy statements where applicable. The modules provide a series of teaching cases, developed aim to be representative of patients seen in primary care, while also allowing for the demonstration of genetics issues and principles.

The cases are intended to serve as a model for engaging medical students' and residents' interests in genetics topics. For each case, questions are noted and a brief discussion is provided. The additional web sites and other references listed provide the basis for more in-depth exploration of each topic.

The eight topics chosen for development of teaching cases are taken from core areas of primary care practice. In the following section – "**How to Use This Curriculum**" – we outline the framework we used in developing these teaching materials, and how we expect them to be used. These teaching modules have been used in pilot projects to introduce genetics into the primary care teaching curriculum, under the leadership of 20 multidiscliplinary teaching teams participating in the GPC project. They have also been reviewed by experts in primary care and genetics for relevance and accuracy. They represent part of an on-going project to develop tools for primary care faculty to assist them in introducing genetics topics into the primary care curriculum. Additional materials will be available in fall 2002, together with updated versions of these modules.

We welcome your comments and suggestions.

GPC Executive Committee
GPC Genetics Consultants
GPC Advisory Committee

# How to Use This Curriculum

The modules in this curriculum include teaching cases in 8 topic areas:

❖ Breast/Ovarian Cancer
❖ Cardiovascular Disease
❖ Colorectal Cancer
❖ Congenital Hearing Loss
❖ Dementia
❖ Developmental Delay
❖ Iron Overload
❖ Ethical, Legal and Social Issues (ELSI)

Each teaching case includes questions and discussion to illustrate genetics themes and diagnoses. Each module also includes references to key documents and useful web sites for additional background information.   The 8 major topic areas were chosen because they are core areas of primary care practice and because they could illustrate a range of genetic issues relevant to primary care practice.   ELSI is presented as a separate module, but is also incorporated into the other modules.  We took this approach because of the attention that has been given in both popular and scientific press to the broader social implications of genetic medicine.  We assume that many of the broader issues raised by genetics have counterpoints in primary care practice; the ELSI cases are intended to provide a basis for identifying these common themes. The discussion provided for the teaching cases are intended as a guide to the teaching points the case raises rather than as a an exhaustive review of the topic or a replacement for critical literature review.  We expect that you will identify additional points that should be made and useful variations on the themes for each case.

The case-based approach, and the concept of teaching materials serving as a bridge between primary care practice and genetics, emerged from discussions of the GPC Advisory and Executive Committees in September 1999 and March 2000.  Based on these discussions, we sought to provide materials that:

• represented patients who would be recognizable to primary care trainees,
• were adaptable to different teaching settings, and
• emphasized connections between genetic and primary care practice, in terms of both clinical skills and philosophy of practice (for example, the value of taking a family history; the importance of evaluating tests in terms of patient outcomes; and the core  value of respecting patient preferences).

The teaching cases should be viewed as raw material, to be used in any combination or setting that proves useful.  They can be used alone or as an accompaniment to didactic material, lectures or seminar discussion, either on a given topic area (e.g. colorectal cancer, developmental delay) or on a particular theme (e.g. patient confidentiality, preventive care).

In developing these materials, we used a framework for integrating genetics issues into primary care practice that emerged from discussions of the GPC Advisory and Executive Committees. The underlying themes of the framework concern the distinction between "thinking genetically" - the concept that a genetic cause will not be found unless it is considered as a possibility - and "acting genetically" - the recognition that a decision to pursue a genetic cause in a particular patient should be determined by its likelihood (estimated from the patient's presentation, and the prevalence of the genetic condition) and the value of the genetic diagnosis in caring for the patient (its treatability, the prognostic or management information provided by the genetic diagnosis, the implications of the genetic diagnosis for the family). This framework identifies the following elements as important to the appropriate use of genetics in primary care:

1. Defining populations at risk/prevalence
   - What genetic conditions are most commonly seen in primary care populations?
   - What indicators (in the patient or in the clinical presentation) increase the likelihood of a genetics explanation?

2. Determining the impact of genetic information on patient outcomes
   - To what extent does a genetic diagnosis lead to a specific preventive or management option?
   - When does genetic information provide unique prognostic information?
   - When/how can genetic information cause harm?

3. Relevance of mode of inheritance
   - Mode of inheritance is key to determining other family members at risk
   - When risk to other family members is high, there may be an obligation or a concern to help the patient inform other family members of potential genetic risk.

4. Cautious approach to genetic testing
   - Genetic tests may provide a means to make a definitive diagnosis, and may be particularly important in identifying inherited risk in family members of an affected individual.
   - However, many genetic tests are complex with limited sensitivity and/or specificity.
   - Needs for pre- and post-test counseling are often detailed, addressing issues of test interpretation (potential for ambiguous test results, as well as false positives and false negatives), implications of test results for clinical management and psychosocially, and implications of test results for family members.

# Breast and Ovarian Cancer

A resident asks....

Why should a primary care doctor know about breast or ovarian cancer genetics?

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**Key Points**:

- Family history is an important tool in the assessment of breast and ovarian cancer risk

- Women are concerned about breast cancer and often over-estimate their risk. They may view themselves as candidates for genetic testing when their likelihood of a positive test is minimal.

- BRCA1/2 mutations are **rare** and there are few data to assess the outcome benefits of interventions to reduce risk

- Testing for BRCA1/2 is mentioned frequently in the medical and lay press. Your patient may ask you about the availability of gene testing for breast cancer

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Learning Objectives for the Breast Cancer Module:

Participants will be able to:

- Evaluate family history information to identify women with an increased risk of breast and ovarian cancer

- Describe important features of autosomal dominant inheritance, including the potential for inheritance of risk through the paternal side

- Use current breast cancer risk assessment models and understand their limitations

- Evaluate management strategies for women with a high risk of breast or ovarian cancer

Web Resources for Genetics of Breast Cancer:

http://www.geneclinics.org
http://cancernet.nci.nih.gov/clinpdq/cancer_genetics/Cancer_genetics.html

**CASE # 1**

Your patient, a 36-year-old woman, recently attended her 15-year college reunion. She talked with her college roommate, who had been diagnosed with breast cancer. Her friend had genetic tests (done after her cancer diagnosis) that indicated she had a genetic predisposition to cancer. Your patient wants to know what she should do. Specifically, she asks if she should get the genetic test her friend got, to determine her own risk. She has checked the Internet and identified a company that offers this testing. She adds that her aunt had breast cancer at age 72.

**Questions for Discussion:**

1. What additional information would be helpful in determining this patient's risk for breast cancer?

2. Assuming she has no additional family history of breast cancer, should BRCA1/2 testing be offered?

**CASE # 1 - Discussion**

1. *What additional information would be helpful in determining this patient's risk for breast cancer?*

Family history represents the most useful tool for identifying women who may have an inherited predisposition to breast cancer. At the same time, *the implications of a positive family history are variable* - many women with a positive family history of breast cancer do not have a risk significantly above average.

Key elements in the family history are as follows (see Pinsky et al, 2001):

1. *Unusual breast cancer history*:

    - 2 or more relative with breast cancer
    - early onset of breast cancer (before age 50)
    - breast cancer in a male relative

2. *Father's side should be checked as well as mother's side* – breast cancer risk can be inherited from either side of the family

3. *Ovarian cancer* is also important - genetic risk typically involves both cancers

When is genetic risk present? *There is no simple, well-defined threshold.* In general, the more family history risk factors present, the greater the likelihood of genetic risk. One expert group (deBock et al, 1999) recommends genetics consultation if family history includes:

> *2+ relatives with breast cancer, at least one affected < 50, or*
>
> *3+ relatives with breast cancer at any age*
>
> (These criteria assume that affected relatives are all in a single biological line (i.e., all on father's side or mother's side).

In addition, if *both breast and ovarian cancer* are present, or if *male breast cancer* is present, the likelihood of a genetic risk is higher for any given level of family history. (Males who carry BRCA1/2 mutations also have an increased risk of prostate cancer; however, prostate cancer is very common, so that a family history of prostate cancer is not highly predictive).

When evaluating family history, it is important to bear in mind that most women with a family history of breast cancer have a modestly increased risk, compared to the general population risk of 10% by age 80 (Feuer et al.1993). Some have may NO increased risk compared to the average: for example, a US study estimated risk based on population-based data and found that breast cancer risk is in the average range for women whose mother or sister developed breast cancer at age 60 or older (the Claus model; see table below).

**Estimated risk of breast cancer according to family history (Claus et al. 1994)**

| Breast Cancer in a Mother OR Sister, Affected at Age: | Risk of Breast Cancer by Age 79 | Breast Cancer In a Mother AND Sister, BOTH Affected at Age: | Risk of Breast Cancer By Age 79 |
|---|---|---|---|
| 20-29 | 21% | 20-29 | 48% |
| 30-39 | 17% | 30-39 | 44% |
| 40-49 | 13% | 40-49 | 35% |
| 50-59 | 11% | 50-59 | 25% |
| 60-69 | 10% | 60-69 | 16% |
| 70-79 | 9% | 70-79 | 11% |

Ovarian cancer risk is also most readily predicted by family history. The table below provides estimates of the *relative risk (RR)* of ovarian cancer according to family history. A RR of 2 indicates a two-fold increased risk compared to women without a family history of ovarian cancer.

**Relative risk of ovarian cancer according to family history (Stratton et al., 1998)**

| Family History of Ovarian Cancer | Relative risk of ovarian cancer |
|---|---|
| Any 1st degree relative with ovarian cancer (mother, sister or daughter) | 3.1 (95% CI 2.6-3.7) |
| Daughter with ovarian cancer<br>Sister with ovarian cancer<br>Mother with ovarian cancer | 1.1 (95% CI 0.8-1.6)<br>3.8 (95% CI 2.0-5.1)<br>6.0 (95% CI 3.0-11.9) |
| More than one affected relative (1st or 2nd degree) | 11.7 (95% CI 5.3-25.9) |
| 2nd degree relative with ovarian cancer (Aunt or grandmother) | 2.5 (95% CI 1.5-4.3) |

**Claus and Gail models for estimating breast cancer risk**

Two empiric models for predicting breast cancer risk, the Claus model (Claus et al. 1994) and the Gail model (Gail et al. 1989) are available. Both have limitations, and the risk estimates derived from the two models may differ for an individual patient. Despite their limitations, they represent the best methods currently available for quantifying breast cancer risk.

**Claus Model**

The Claus model projects the probability of developing breast cancer for women with a family history of breast cancer; the **Table** on page 4 provides an example of risk estimates using this model. It is based on empiric data from the **Cancer and Steroid Hormone Study** (Claus et al, 1994). This model assumes that inherited risk is attributable to a rare autosomal dominant mutation with high penetrance (that is, almost all people who have the mutation get the disease). The risk estimate is based on a woman's current age; the number of first-degree and second-degree relatives with breast cancer (up to two); and their age of onset. The model provides cumulative risk estimates for several different family history configurations. It does not take other risk factors into account and thus may underestimate risk for women with behavioral factors, or reproductive histories that increase risk. It provides useful estimate for most women with a positive family history of breast cancer, but is not suitable for use with women who have three or more relatives with breast cancer.

**Gail Model**

The Gail model projects the probability of developing breast cancer (both invasive and non-invasive) based on some of the known non-genetic risk factors as well as limited family history information. It is based on the major predictors of risk identified in the **Breast Cancer Detection Demonstration Project** study (Gail et al, 1989). Risk factors utilized in the Gail model include current age, age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia, and number of first-degree relatives (mother or sister) with breast cancer (categorized as 0,1 or 2+). It does not consider second-degree relatives, paternal relatives, or *importantly,* the age of onset of breast cancer in the affected relative. It thus may overestimate risk in women whose mothers or sisters had breast cancer at an elderly age and underestimate risk for women who have second-degree relatives with early breast cancer. The Gail model has been validated as a predictor of breast cancer risk in women who adhere to

regular mammography screening (Bondy et al. 1994; Speigelman et al. 1994). Validation studies indicate that the model overestimates risk in women who do not get screened regularly. The reasons for this discrepancy are not clear. It could reflect a selection bias in favor of higher risk among women who participated in the studies from which the Gail risk estimates were made; or it could reflect the increased detection in screened women of lesions that are unlikely to progress to clinical cancer (e.g., small, slow-growing cancers or DCIS).

The Gail model is the basis for the **Breast Cancer Risk Assessment Tool**, a computer program that is available from the National Cancer Institute by calling the **Cancer Information Service** (1-800-4-CANCER). This version of the Gail model estimates only the risk of invasive breast cancer. This same model was used to determine subject eligibility in the NSABP Tamoxifen Breast Cancer Prevention Trial.

### Identifying inherited risk - BRCA1/2 mutations

The women at highest risk of both breast and ovarian cancer are those with an inherited autosomal dominant risk for breast/ovarian cancer – e.g., risk based on the presence of a BRCA1 or BRCA2 mutation. These mutations are rare: prevalence is estimated to be about 1/800. As noted above, examination of the details and pattern of the family history is the most useful approach for identifying women who are likely to carry such mutations (Biesecker et al. 1993; Ford et al. 1995). **CancerGene** software includes a tool for assessing the likelihood of a mutation, using family history data (http://www.swmed.edu/home_pages/cancergene/).

2. *Assuming she has no additional family history of breast cancer, should BRCA1/2 testing be offered?*

In addition to family history of breast cancer, a family history of ovarian cancer is relevant. Assuming there is no history of ovarian cancer and no further history of breast cancer (including none on her father's side), the patient's risk to have breast cancer based on her family history is similar to that of an average risk woman, according to the Claus model. Indeed, her risk would be in the average range even if her mother, rather than her aunt, had had breast cancer in her 70s

(see **Table** page 4). It would be difficult to justify BRCA1/2 testing in this setting. Her likelihood of having a negative test result is very high, and could lead to a mistaken belief that her negative test result lowered her risk. In fact, her pre-test risk would not be changed by a negative test result, because she is not expected to be carrying a cancer-predisposing mutation.

Other risk factors, such as those assessed in the **Breast Cancer Risk Assessment Tool**, could provide additional information about her risk. Note, however, that her family history of an aunt with breast cancer (a second degree relative) would not be considered positive in the Gail model on which this tool is based. In the absence of family history, her Gail model risk would not be elevated unless she had a history of prior dysplasia on breast biopsy or lobular carcinoma *in situ*. Such history of breast disease would probably already have led to an appropriate follow-up plan for breast surveillance.

**Common over-estimate of breast cancer risk**

The patient may benefit most from a discussion of risk that allows her to recognize her average lifetime risk, and, given her age, her very low short-term risk. A review of recommended breast cancer prevention strategies may also be helpful (mammography, breast self-exam and clinician exam).

An important context for this case is that women commonly misunderstand their risk of breast cancer. Many over-estimate their lifetime risk to a significant degree (Alexander et al. 1996; Black, Nease & Tosteson 1995; Bunker, Houghton & Baum 1998; McCaul et al. 1998; Pilote & Hlatky 1995) and over-estimate the proportion of female deaths attributable to breast cancer as well (Black, Nease & Tosteson 1995; Gallup Survey 1995). In addition, women often see breast cancer as a risk of young women. In one survey, for example, women between 40 and 50 over-estimated their short-term risk of dying from breast cancer by 22-fold and their lifetime risk by 12-fold (Black, Nease & Tosteson 1995). Many women also have the mistaken belief that their risk diminishes as they get older (Dolan, Lee & McDermott 1997; Fulton, Rakowski & Jones 1995). Taken together, these misperceptions of risk can be a cause of undue anxiety among younger women and of failure to complete mammography screening among older women.

**CASE # 2**

A woman of Ashkenazi Jewish descent asks about the "breast cancer gene." She has been reading in the papers that Jewish women may be more at risk. Her cousin and grandmother both had breast cancer, but they are on her father's side, so she assumes their cancers do not affect her risk. Clarification of her family history reveals that her paternal grandmother had breast cancer at age 42. A first cousin (daughter of a paternal aunt) had breast cancer at age 45.

**Questions for Discussion:**

1. What counseling should be provided regarding her family history of breast cancer?
2. Assuming she has no additional family history, should BRCA1/2 testing be offered?

**CASE #2 - Discussion**

*1. What counseling should be provided regarding her family history of breast cancer?*

Her family history raises the possibility of an inherited breast cancer predisposition on her father's side. The patient has articulated a common misunderstanding, that a family history of breast cancer is important only if it is present on the mother's side. In fact, the cancer predisposition can be passed on by either the father or the mother (see Review of family history characteristics associated with BRCA1/2 mutations below). Two additional comments can be made about her family history. If a cancer-predisposing mutation is present, both her affected relatives (her grandmother and her cousin) probably carry it, based on their age of diagnosis. If this is the case, her cousin's mother (her paternal aunt) is an unaffected mutation carrier – a phenomenon that has been described for both BRCA1 and BRCA2 mutations.[1] If a mutation is present, her father has a 50% chance of carrying it, and as a result, the patient has a 25% chance of inheriting it.

**Review of family history characteristics associated with BRCA1/2 mutations (autosomal dominant inheritance)**

- The cancer predisposition is passed from one generation to the next ("vertical transmission").
- Each child of a person with the inherited predisposition has a 50% chance of inheriting the predisposition.
- Males and females inherit the cancer predisposition with equal frequency.
- Male carriers will usually not be affected, that is, the cancer predisposition is largely sex-limited. However, they can still pass the predisposition on to their children as above. Men with BRCA2 mutations have a 60-fold increased risk of developing breast cancer increased (from 0.10% to 6%).
- Lifetime cancer risk may be very high in those who inherit the cancer predisposition but appears to be subject to modifying factors - e.g. lifetime risk of breast cancer associated with BRCA1 mutations has been estimated to range from 37%-85%.

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[1] As an alternative explanation, the grandmother and cousin could carry different mutations, with the cousin inheriting a mutation from her father. This situation has been observed in Ashkenazi Jewish families, where the

- Inherited risk for breast cancer is usually associated with inherited risk for ovarian cancer. Other cancer risks may also occur, including an increased risk of prostate cancer in males.

The most important issues to address in counseling the patient about a potential inherited risk are her understanding of inherited cancer risk, her concerns and worries, and the options available to her to reduce risk (see the Discussion for Question # 2 below).  People vary in the value they place on knowing about genetic risk.  For some, the possibility of an inherited cancer predisposition provides a powerful motivation to be tested.  Others feel less motivation to pursue such knowledge, and some find it threatening.  The patient's age may influence her decision.  If she is 50 years old, already having regular mammograms, and uninterested in interventions such as prophylactic surgery, she may feel no urgency to pursue the question of inherited risk.  *If she is 38, knowledge about risk may change her screening decisions.*  It is important to address the patient's assessment of her own personal risk and the impact of her learning that the family history on her father's side is pertinent to her own risk.

Pursuing genetic testing involves a number of complex issues as outlined in question 2 below.  Testing may or may not be informative, and should ideally start with an affected family member.  A positive result would have implications both for herself and for her children.  All of these issues may influence the patient's thinking about cancer risk and interest in pursuing genetic testing.  Discussion of inherited cancer risk might ideally occur over several visits, giving the patient time to absorb information.  Other family members on the paternal side of the family might also benefit from genetic counseling at some point in the future, to discuss genetic testing options.

*2.  Assuming she has no additional family history, should BRCA1/2 testing be offered?*

The phrasing of the question as "should the test be offered?" as opposed to "recommended" represents the two dynamics of the testing decision. 1) Is there a justification for the testing based on her estimated risk, and 2) how do the benefits and risks of testing coincide with the patient's reasons for testing and management decisions she would make based on the results?

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cumulative prevalence of BRCA1/2 mutations is about 2.5% due to 3 relatively common mutations (Roa et al.

It is reasonable to offer testing to this patient; however the offer of testing is actually to the patient's family, as testing should be offered first to an affected family member. In addition, the results of the test will affect more than just the patient. The likelihood of a BRCA1 or BRCA2 mutation in the family is approximately 20%, based on empiric data reported by Myriad Laboratories, the company that offers testing (http://www.myriad.com/gtmp.html). Factors contributing to this estimate are the presence of two family members with breast cancer under age 50 and the Ashkenazi Jewish ethnicity. Three cancer-predisposing mutations (two in the BRCA1 gene and one in the BRCA2 gene) are relatively common in women of Ashkenazi Jewish descent (Jews of Central and Eastern European ancestry), with a cumulative prevalence of about 2.5% (Roa et al. 1996); as a result, Jewish women with significant family history have a higher likelihood of carrying BRCA1/2 mutations than non-Jewish women.

In offering the test to the patient, the benefits and risks of testing as outlined below should be discussed so that the patient can make an informed decision on whether or not to pursue testing.

**Why test?**

Genetic testing offers the opportunity to identify individuals with an increased risk of cancer. This risk information may be helpful in planning decisions about cancer screening or use of prophylactic surgery; some people may want to use information about their personal risk in making family planning or career decisions. However, *evidence on the efficacy of interventions to reduce risk is limited.* The decision to be tested is thus a subjective one, in which risks and benefits must be weighed in terms of personal values and preferences, in light of many uncertainties. Genetic testing also offers the opportunity to determine which family members have not inherited the cancer predisposition present in the family.

**Who should be offered testing?**

The most appropriate candidates for testing are those who have a high likelihood of carrying a genetic susceptibility to cancer -- i.e., individuals from cancer-prone families showing

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1996).

characteristics of autosomal dominant inheritance.  Estimates of the likelihood of finding a

BRCA1 or BRCA2 mutation based on family history can be obtained from the **Cancer Gene**

web site (http://www.swmed.edu/home_pages/cancergene/) or from data based on the experience

of the laboratory offering the testing (http://www.myriad.com/gtmp.html).

**Optimal testing strategy**

1.   Test one or more affected relatives.

2.   If a mutation is identified, testing for this specific mutation can be offered to unaffected
     family members at a much lower cost.

3.   If an individual does test positive, follow-up counseling should include discussion of
     interventions to reduce risk (see **Table**, page 13)

**Why test an affected relative first?**

If a mutation cannot be identified in an affected family member, further testing will be non-

informative and should not be pursued.  However, if a mutation can be identified in an affected

relative, both negative and positive test results will be informative in unaffected family members.

**Need for counseling (Biesecker et al. 1993; Geller et al. 1997)**

Genetic testing involves potential risks as well as benefits.  Individuals contemplating testing

should have the opportunity to consider these issues carefully prior to deciding whether or not to

be tested. Knowledge of an inherited predisposition may cause anxiety and family distress, and

may also pose a risk for loss of insurance or employment opportunities.

**Preventive care options for carriers of BRCA1 and BRCA2 mutations**

The benefits of tailored preventive care for individuals with an inherited predisposition to breast

and/or ovarian cancer are largely unproven.  Most recommendations are made on the basis of a

presumed benefit for individuals with a high lifetime risk of cancer (see **Table,** next page).

**Table. Interventions to reduce risk in women with BRCA1/2 mutations**

| Intervention | Quality of Evidence |
|---|---|
| **Breast Cancer Surveillance** | |
| • Breast self-exam<br>• Clinical breast exam, annually or semiannually, beginning at age 25-35<br>• Mammography, annually beginning at age 25-35 | A consensus panel has recommended early initiation of mammography screening based on expert opinion (Burke et al. 1997). **No systematic study of the risks and benefits of early screening are available**. |
| **Ovarian Cancer Surveillance** | |
| • Pelvic examination, q 6-12 months, beginning age 25-35<br>• Transvaginal US with color doppler and serum CA-125 level, q 6 -12 months, beginning age 25-35 | A panel has recommended ovarian cancer screening based on expert opinion (Burke et al. 1997). **Studies of these screening methods have not demonstrated outcome benefit and have demonstrated limited sensitivity and specificity**. |
| **Preventive Surgery** | |
| • Breasts: Prophylactic bilateral simple mastectomies $\pm$ reconstruction | **A panel has recommended the *offer* of prophylactic mastectomy** based on expert opinion (Burke et al. 1997). A retrospective study of prophylactic mastectomies performed at the Mayo Clinic study estimated a 90% reduction in breast cancer risk from the procedure (Hartmann et al. 1999). A subset analysis of BRCA1/2 mutations carriers, reported but not yet published, indicates a similar benefit for this group. |
| • Ovaries: Prophylactic bilateral oophorectomy after completion of desired reproduction | **A panel has recommended the *offer* of prophylactic oophorectomy** based on expert opinion(Burke et al. 1997). A small observational study with limited power found no statistical difference in the incidence of ovarian cancer between those that had or did not have an oophorectomy (Struewing et al. 1997). |
| **Chemoprevention** | |
| • Tamoxifen | **No evidence-based recommendation for BRCA1/2 mutation carriers can be made at this time.** A US randomized trial of women selected on the basis of the Gail model (Gail et al. 1989) demonstrated ~ 50% reduction in breast cancer risk over 4 years (Fisher et al. 1998). A smaller UK trial, using more stringent family history criteria for subject selection, failed to demonstrate benefit (Powles et al. 1998). |

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# Cardiovascular Disease

A resident asks....

> Why should a primary care doctor want to know about genetics and cardiovascular (CV)
> disease?

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**Key Points**:

- CV disease is common.

- Coronary heart disease (CHD) results from an interplay of genetic and environmental factors.

- Relatively uncommon genetic disorders can dramatically increase the risk of heart disease,
  and its occurrence at an earlier age.

- Interventions are effective at reducing morbidity and mortality.

- A family history may identify others who would benefit from screening and preventive
  interventions.

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Learning Objectives for Cardiovascular Disease Module

Participants will be able to:

- Understand what constitutes a positive family history.

- Understand how family history helps to identify autosomal dominant CV disease.

- Understand how different screening protocols influence the importance of obtaining family history.

- Understand the need to consider prevention efforts for family members, whether positive family
  history is based on lifestyle or genetics.

**CASE #1**

A medical student you are precepting in clinic wants to know if she should check a cholesterol level on a 25-year-old man who is establishing care. The patient is a vegan who exercises regularly. He has no history of smoking, hypertension or diabetes. However, he has a family history of heart disease; his father had a heart attack at age 50. He notes that his father was overweight, ate a high fat diet and never exercised.

**Questions for Discussion:**

1. What is the relevance of the family history of heart disease for this patient?
2. Does the role of family history in clinic decision making change depending on the screening criteria used – American College of Physicians (ACP), U.S. Preventive Services Task Force (USPSTF) or National Cholesterol Education Program (NCEP)?

**CASE #1 – Discussion**

*1. What is the relevance of the family history of heart disease for this patient?*

A family history of early CHD increases personal risk.  A search for modifiable risk factors is indicated. In particular, elevated cholesterol should be suspected in anyone with a strong family history of premature CHD, which **National Cholesterol Education Program** (NCEP) defines as a family history of premature CHD or sudden death occurring in a first degree female relative less than 65 years old or in a first degree male relative less than 55 years old (see **Table 1**).

Epidemiological, observational and interventional studies clearly demonstrate a causal role of hypercholesterolemia in CHD, a condition that affects approximately 7 million Americans and is the most common cause of death in both men and women in the United States.  The risk of CHD rises 2-3% for every 1% increase in total serum cholesterol.  Twenty percent of adult Americans have a cholesterol level of greater than 240 mg/dL, which in a middle-aged man indicates a 9-12% risk of developing symptomatic coronary artery disease within 7- 9 years.  In general, elevated LDL cholesterol and inversely low HDL cholesterol are associated with higher risk of coronary events.  Risk can be further defined by analysis of other factors such as lipoprotein(a) [Lp(a)].   Some data suggests that an elevated triglyceride level is an independent risk factor for coronary artery disease (Austin et al, 1998). Additionally, non-lipid cardiac risk factors such homocysteine, fibrinogen and c-reactive protein levels may influence risk status (Harjai, 1999).

Because of the association between cholesterol and increased CHD risk, routine screening of adults for hyperlipidemia is recommended by many advisory groups.  The **US Preventive Services Task Force** (USPSTF) and **American College of Physicians** (ACP) recommendations (see **Tables 2.1, 2.2**) reflect concern about the potential risks of lipid lowering medication and suggest delaying the age of onset of laboratory cholesterol screening in order to focus screening on higher risks groups in whom the benefit-risk ratio and cost-effectiveness is greater. The **NCEP Adult Treatment Panel III** guidelines (see

**Table 2.3**) take a more aggressive approach to screening while recognizing the different risk-benefit ratios in primary and secondary prevention.

The NCEP definition of positive family history, intended to identify genetic risk for hyperlipidemia, is somewhat arbitrary but necessary for institution of national guidelines. In reality, a positive family history is a more ambiguous entity that takes into account both the interactions of lifestyle and genetics and the family structure, i.e. the number of relatives at risk and their biological relationship to the person whose risk is being assessed. For example, a history of early CHD in a parent may reflect a genetic predisposition, a mix of non-genetic risk factors, or both. Effective early prevention may result in a parent with a history of medically treated hypercholesterolemia rather than myocardial infarction. A strong family history on the mother's side may be more evident in her male relatives than in her own medical history, due to the later onset of disease. Family history information should be evaluated with these considerations in mind.

A small number of families have genetic conditions conferring very high risk of CHD – e.g., familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH). These are autosomal dominant traits that cause a markedly increased risk of CHD with the first myocardial infarction occurring at a mean age of 40 years old in affected men and 10 years later in affected women. In familial hypercholesterolemia, an LDL receptor defect often results in cholesterol levels above 300 mg/dL. Familial hypercholesterolemia (seen in 1 in 500 people in its heterozygous state) causes 5% of myocardial infarctions occurring before age 60. In familial combined hyperlipidemia, estimated to occur in 1 in 100 people, increased production of apoprotein B causes elevated levels of triglycerides, cholesterol, or both. Approximately 15% of individuals with myocardial infarction before age 60 have familial combined hyperlipidemia (see Summary **Table 3**). While most individuals are identified with FH by a family history of premature CHD, the condition may occasionally be noted on physical exam by noting tendinous xanthomas, commonly found on the extensor tendons of the hand or as thickening ( >7 mm) of the Achilles tendon, which are pathognomonic for familial hypercholesterolemia.

2. *Does the role of family history in clinic decision making change depending on the screening criteria used – American College of Physicians (ACP), U.S. Preventive Services Task Force (USPSTF) or National Cholesterol Education Program (NCEP)?*

The importance of a positive family history as a basis for screening or prevention efforts differs depending on the protocol the physician is using. According to ACP or USPSTF recommendations, men younger than 35 and women younger than 45 are screened for lipid disorders only if they are at increased risk, primarily assessed by a positive family history. Because NCEP recommends that all individuals be screened for lipid disorders beginning at age 21, the family history is not important in the decision to screen. However, family history does influence the interpretation of cholesterol level and management decisions.

The ACP and USPSTF lipid screening guidelines are based on studies indicating that beginning treatment at age 35 for men and age 45 for women results in a decrease in morbidity and mortality nearly equal to that of treatment started at an earlier age, and avoids unnecessary years of the costs and potential adverse effects of medication (Law et al, 1994). However, this result cannot be extrapolated to the relatively small number of people with FH or FCH because their risk of CHD begins early in adult life, underscoring the importance of using family history to identify them. Screening for smoking and hypertension is recommended for all adults, starting in early adulthood. Similarly counseling about a healthy lifestyle – regular exercise, low fat diet and avoidance of smoking – is recommended. However, the effect of such advice is not clear. One might expect that knowledge of increased risk would motivate behavioral efforts, but compliance with recommendations for lifestyle modifications is not significantly increased based on knowledge of one's cholesterol level (Elton et al. 1994; Hanlon et al. 1994; Robertson et al. 1992; Strychar et al. 1998).

Knowledge of genetic risk may be different from information about other risk factors. In a pilot study of the parents of 24 children with neonatal screening test result showing the child to be at increased risk of FH, the parents responded differently depending on their perception of the underlying cause of this risk. When they perceived the test as detecting raised cholesterol, their child's condition was seen as

"familiar, dietary in origin, controllable and less threatening." When it was viewed as a genetic problem, it was seen as "uncontrollable and, hence, more threatening" (Senior, Marteau & Peters 1999). These preliminary results suggest the need to consider the effect of a sense of fatalism that may be attached to risks perceived as genetic in origin.

**CASE #2**

A 47-year-old normotensive, non-diabetic man is admitted with an acute MI.  After his hospitalization and subsequent recovery, he is found to have an elevated cholesterol of 300, HDL 35, LDL-C 195, TG 350.  He is obese and smokes one pack per day and eats a high fat diet.  He does not exercise.  He has two younger brothers who have similar lifestyles.  Family history is unknown, as they were raised by godparents after their parents were killed in an auto accident.

**Questions for Discussion:**

1.  What are the likely contributors to his cardiac risk status?
2.  Should you encourage the patient to disclose his health status (and its implications for risk to others in the family) to his family members?

**CASE #2 – Discussion**

*1. What are the likely contributors to his cardiac risk status?*

In assessing cardiac risk in general, age is the best predictor of death from CHD, with a 100-fold increase between ages 40 and 80. Other established risk factors for CHD include dyslipidemia, hypertension, diabetes, and cigarette smoking. In addition, gender is a factor: women tend to develop CHD later than men. For a non-smoking, normotensive 55-year-old man with a total cholesterol level less than 200 mg/dL, the probability of having a heart attack within 8 years is 31/1000. If he smokes, the risk is 46/1000; if he has high cholesterol (>260 mg/dL) and smokes, it is 64/1000. With the addition of hypertension (systolic greater than 150 mmHg) to smoking and hypercholesterolemia, his risk of myocardial infarction within 8 years is 95/1000.

*2. Should you encourage the patient to disclose his health status (and its implications for risk to others in the family) to his family members?*

Because knowledge of a family history of FH or FCH influences screening and treatment decisions, it has the power to reduce events. Providers are encouraged to inform their patients to notify family members of the potential impact of their own health status on risk to biologic relatives. The patient's lipids raise the possibility of these genetic diagnoses. More likely, his lipids reflect his poor dietary habits, obesity and sedentary lifestyle. (Background genetic factors – normal variants in genes coding for apolipoproteins and other proteins related to lipid metabolism – probably contribute as well.)

Whether his CHD is due primarily to genetics or primarily to lifestyle, his family members are likely to benefit from information about cardiac risk reduction. Because discussions about talking to family members about risk have occurred primarily in the genetic community, less attention has been paid to the opportunity to use one patient's health status as a springboard to educate other family members about risk, and, in particular, about the impact of lifestyle on health. Yet lifestyle, like genetics, is often shared among family members.

**CASE #3**

A 40-year-old woman sees you to help direct her exercise and weight loss program. She is a non-smoker, has no diabetes or hypertension, and her BMI is 24.  Her 62-year-old mother just died of a heart attack, and her brother was found to have elevated cholesterol. You obtain a fasting lipid profile that shows her LDL to be 142 and her HDL is 45.  She tells you that according to the 1993 NCEP guidelines, she understands she doesn't need medications, but wonders whether newer data will prompt more strict guidelines.  She'd also like you to explain the genetics of heart disease.

**Questions for Discussion:**
1.  What is the appropriate management strategy for her?
2.  What information about genetic risk is most relevant to her care?

**CASE #3 - Discussion**

*1. What is the appropriate management strategy for her?*

Although the patient is correct that NCEP III guidelines are stricter than previous NCEP guidelines (see **Table 2.3**), it is not clear that she should pursue more aggressive therapy. She falls into the 0-1 risk factor category (her one risk factor is her mother's heart attack). Thus her LDL goal, according to NCEP III, is < 160, which she has met (**Table 2.4**). With an additional risk factor (e.g., if her brother were to develop CHD, or she were to develop hypertension – or if she were ≥ 55 years), her NCEP III LDL goal would be ≥ 130. Thus no additional management is indicated now, but continued careful monitoring of cardiac risk factors is appropriate.

*2. What information about genetic risk is most relevant to her care?*

The patient may benefit from learning that the genetics of heart disease are complex. Both rare high risk mutations and relatively common genetic variants contribute to CHD risk. Many of the "background" common genetic variants influence the likelihood of developing risk factors such as hypertension or diabetes.

Personal efforts to reduce risk are helpful no matter what genetic risk is present: People with FH, for example, benefit significantly from avoiding smoking, exercising regularly, etc. This patient's family history (her mother's heart attack) points to an element of genetic risk. Her own efforts with exercise and diet are likely to be very helpful in further reducing her personal risk.

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**Table 1**

# FOR PEOPLE WITH INCREASED TOTAL CHOLESTEROL

## NCEP III risk factors used in determining goals for LDL

### POSITIVE FACTORS (raise risk)

*NON-MODIFIABLE*

**Age**: men ≥ 45 years, women ≥ 55 years or
premature menopause without estrogen replacement

**Family hx of premature CHD**
CHD / sudden death in 1° female relative <65 year
or in 1° male relative <55 years

*MODIFIABLE*

**Cigarette smoking**

**Hypertension**: ≥140/90 mmHg or treated

**HDL** < 40 mg/dl

**Diabetes mellitus**

### NEGATIVE FACTOR

**High HDL** ≥ 60 mg/dl     (If present, negates one positive risk factor in above determination)

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Of note: Obesity and inactivity, while not considered risk factors in NCEP III classification, are seen as areas of intervention.

| Table 2.1 | **American College Of Physicians - 1996 Cholesterol Screening Guidelines** |
|---|---|

**Primary Prevention**

**Target population**
**Middle-aged Adults\***

　　　　Men - age 35-65 years　　　　　　　Women - age 45-65 years

**Selective screening of young adults** with history or physical examination suggesting a familial lipoprotein disorder or at least 2 other risk factors for coronary heart disease

**Recommended approach**

Screening of total cholesterol is not mandatory but is considered an appropriate strategy if done. Abnormal results should be confirmed with a repeat test.

**Frequency: variable, depending on test results**

If results normal, test once.
If results near treatment threshold, repeat at least every 5 years.

**Secondary Prevention**

**Recommended approach**

Screening with a lipoprotein analysis is recommended for any patient with a prior event.

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| Table 2.2 | **U.S. Preventive Services Task Force - 1995 Cholesterol Screening Guidelines** |
|---|---|

**Primary Prevention**

**Target population**
**Middle-aged Adults\***

　　　　　　Men - age 35-65 years　　　　　Women - age 45-65 years

**Selective screening of young adults** with family history of very high cholesterol or premature coronary artery disease; or with other major risk factors for coronary heart disease

**Recommended approach**
Screening of total cholesterol recommended.
Abnormal results should be confirmed with a repeat test.

**Frequency: variable, depending on test results**
If results normal, test at least once.
Periodic screening most important during times of cholesterol increase
(middle-aged men, perimenopausal women, weight gain).

**Secondary Prevention**

**Recommended approach**

Screening with a lipoprotein analysis is recommended for any patient with a prior event.

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**Table 2.3  NCEP Adult Treatment Panel III Cholesterol Screening Guidelines
(http://www.nhlbi.nih.gov/guidelines/cholesterol/)**

**Step 1:**   Determine lipoprotein levels (LDL, total and HDL cholesterol) obtained after 9-12 hour fast

Optimal LDL = < 100;  near optimal = 100 – 129

**Step 2:**   Identify whether CHD or CHD-equivalent* is present

* peripheral artery disease, abdominal aortic aneurysm

**Step 3:**   Identify whether other CHD risk factors are present

- smoking

- BP $\geq$ 140/90 or on BP meds

- HDL < 40

- Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first degree relative < 65 years)

- Age (men $\geq$ 45 years; women $\geq$ 55 years)

**Step 4:**   If 2+ risk factors (other than LDL $\geq$ 130), assess 10-year CHD risk (Web site refers reader to

Framingham tables; most people with 0-1 risk factors have 10-year risk < 10%)

**Step 5:**   Determine risk category to establish goals of therapy (see **Table 2.4**)

**Step 6:**   Initiate lifestyle changes

**Step 7:**   Consider adding drug therapy if LDL remains above goal

**Step 8:**   (After 3 mos. of lifestyle changes)

Identify metabolic syndrome (defined by 3 or more of elevated waist circumference; elevated

triglycerides; low HDL; BP $\geq$ 130 / $\geq$ 85; fasting glucose $\geq$ 110).

**Step 9:**  Treat elevated triglycerides ($\geq$ 150) through intensified weight management and increased physical

activity

| Table 2.4   LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories (http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm/) | | | |
|---|---|---|---|
| **Risk Category** | **LDL Goal** | **LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)** | **LDL Level at Which to Consider Drug Therapy** |
| CHD or CHD Risk Equivalents (10-year risk >20%) | <100 mg/dL | ≥100 mg/dL | ≥130 mg/dL (100-129 mg/dL: drug optional)* |
| 2+ Risk Factors (10-year risk ≤20%) | <130 mg/dL | ≥130 mg/dL | 10-year risk 10-20%: ≥130 mg/dL <br><br> 10-year risk <10%: ≥160 mg/dL |
| 0-1 Risk Factor** | <160 mg/dL | ≥160 mg/dL | ≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional) |

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

** Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

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# Colorectal Cancer

A resident asks....

Why would a primary care doctor want to know about the genetics of colorectal cancer?

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**Key Points**:

- About 10% of people have a family history of colorectal cancer.  These people are candidates for early initiation of routine colorectal cancer screening (at age 40 instead of age 50) and might be considered for more aggressive screening strategies.

- The typical primary care practice, 2 to 8 patients (1/200 – 1/800) are from "high risk" families, with a condition called hereditary nonpolyposis colorectal cancer (HNPCC).  These patients are have a high lifetime risk of colorectal cancer, with risk starting in their 20s, and have an increased risk for other cancers as well.

- Rarely, primary care practitioners will see patients with a family history of familial adenomatous polyposis (FAP).  Patients who have inherited this condition are candidates for prophylactic colectomy.

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Learning Objectives for Colorectal Cancer Module:

Participants will be able to:

- Understand the family history characteristics associated with increased colorectal cancer risk and with inherited colorectal cancer syndromes.
- Understand the rationale for early and more aggressive colorectal cancer screening in people with a positive family history.
- Understand the implications for patient confidentiality when family members receive care at the same health care facility.
- Understand the rationale for the claim that health care providers may have a duty to disclose information about genetic risk to family members.

**CASE # 1**

A resident presents a 42-year-old woman who has come for an annual exam. The resident has performed routine health maintenance, including a pelvic examination with Pap test and a clinician breast exam; a dT booster has been ordered. The patient is a non-smoker, drinks minimal alcohol, and has no known family history of breast, colorectal or ovarian cancer. The resident asks if any other preventive care is indicated.

You are aware that the patient's 50-year-old sister (who is your patient) recently underwent surgery for a small Stage 1 colorectal cancer, found as a result of routine colorectal cancer screening.

**Questions for Discussion:**

1. How would this information (if known to the current patient) affect your advice about preventive care?
2. What ethical concerns are raised by this case?
3. After discussing this case in a post-clinic conference, you and your colleagues realize that no one in the practice routinely counsels patients diagnosed with colorectal cancer to discuss their diagnosis with family members. Should a change be made?

**CASE #1 – Discussion**

1.  *How would this information affect your advice about preventive care?*

(a)  Because the patient has a first degree relative with CRC at age 50, her lifetime risk is estimated to be about 2x higher than average risk. She may be a candidate for screening starting at age 40.

About 5-10% of people have a first degree relative (parent, sibling or child) with colorectal cancer. This family history increases the risk of colorectal cancer by about two-fold compared to no family history of colorectal cancer. In addition, cancer tends to occur earlier in people with a positive family history. The cancer risk for a person at age 40 who has an affected first-degree relative is approximately the same risk as the average risk for a person at age 50 (Fuchs et al. 1994). When the relative risk is analyzed in different age groups, the increased risk is found to be more pronounced at younger ages (Fuchs et al. 1994), e.g. before 50, at a time when routine screening is not recommended. There is a consensus that routine screening should begin at age 50 for people of average risk (US Preventive Services Task Force 1996, Winawer et al. 1997, Byers et al. 1997). Thus, the risk related to family history suggests that there may be a benefit in beginning colorectal screening at an earlier age when a positive family history is present – e.g., at age 40. Winawar et al. (1997) note that: "People with a close relative (sibling parent or child) who has had colorectal cancer or an adenomatous polyp should be offered the same options as average risk people but beginning at age 40 years," and "special efforts should be made to assure that screening takes place" if the relative was affected at an early age.

**RATIONALE** (Winawer et al. 1997)
*   Higher risk and earlier onset of cancer in people with an affected first degree relative
*   Evidence for benefit of screening in average risk populations (Level I for FOBT, Level IIA for flexible sigmoidoscopy)
*   Screening test performance assumed to be the same at age 40 as at age 50.

Other experts also recommend more aggressive screening. For example, the **American Cancer Society** (Byers et al. 1997) recommends early screening when a first degree relative has had colorectal cancer or an adenomatous polyp before age 60; initiation of screening is recommended either at age 40 or 10 years before the youngest case in the family, whichever is earlier. The screening strategy recommended is a *full colon screen* every 5 years.

(b) It is appropriate to ask about additional family history as well, because additional affected second-degree relatives (grand-parents, aunts, uncles) would raise the possibility of an inherited colorectal cancer syndrome.

Two rare conditions account for most high risk colorectal cancer families: **Familial Adenomatous Polyposis** (**FAP**) and **Hereditary Nonpolyposis Colon Cancer** (**HNPCC**) (See **Table 1** for prevalence and lifetime risk; See **Table 2** for summary of FAP and HNPCC). FAP is diagnosed by the presence of multiple colon polyps. HNPCC is diagnosed by pedigree characteristics, after FAP has been ruled out. The pedigree criteria that suggest an inherited risk of colorectal cancer include:

- Multiple relatives with colorectal cancer
- Sequential generations affected
- One or more family members affected at an early age (e.g. before age 60)
- Other cancers that are associated with a genetic predisposition, especially uterine (endometrial) cancer
- Multiple primary tumors – e.g., two or more colorectal neoplasms

It is important to recognize that other cancers besides colorectal cancer can be important clues to HNPCC; focusing only on colorectal cancer may miss some families. Other HNPCC-associated cancers include endometrial cancer (~40% lifetime risk in HNPCC) and cancers of the ureter/renal pelvis and small bowel (Vasen et al. 1999).

Identification of an inherited colorectal cancer syndrome has implications for prevention strategies and genetic testing (see Discussion below).

*2. What ethical concerns are raised by this case?*

The patient is apparently unaware of her sister's diagnosis. This may indicate that her sister does not wish to disclose her cancer diagnosis. Yet the information may be important to the resident's patient as a basis for early initiation of colorectal cancer screening. The ethical concerns include:

- Obligation to protect the confidentiality of the sister's medical condition
- Obligation to provide the best care recommendations to the resident's patient

These obligations are potentially conflicting, and may be more difficult to address because of the teaching role of the attending physician.

**Confidentiality**

Physicians are obligated to respect the confidentiality of medical information. In this case, the attending physician has information that may be of value in the care of the resident's patient, but s/he is not free to make it known to that patient without permission. The attending physician may choose to contact the sister recently diagnosed with CRC in order to discuss with her the potential value of sharing her diagnosis with her sister. This conversation will enable the attending physician to determine whether information about the diagnosis was withheld or whether it was simply not apparent to the patient with CRC that her medical history would be relevant to family members.

**Potential duty to disclose**

If there is agreement that the resident's patient should have CRC screening, on the basis of her sister's diagnosis of CRC at age 50, then the health care providers (attending and resident) may have an obligation to ensure that the family history and its implications are disclosed. Family members may also have an obligation to share information that could affect the health care decisions of their relatives. This putative duty **assumes that an action can be taken on the basis of the disclosed information that will improve health outcome.** There is no duty to

disclose family history if it will not lead to a specific action – thus, if the resident's patient were herself over 50 and already a candidate for CRC screening on the basis of age, this case would not raise the same concerns. Similarly, if a health care system reviewed the current evidence on CRC screening and decided on a screening policy that did not include early screening on the basis of a family history of CRC, it could argue against the need for the affected sister to disclose her cancer diagnosis. However, this conclusion would run counter to two published practice guidelines (Winawer et al., 1997; Byers et al., 1997).

3. *After discussing this case in a post-clinic conference (following a discussion with the patient's sister and subsequent disclosure of the family history), you and your colleagues realize that no one in the practice routinely counsels patients diagnosed with colorectal cancer to discuss their diagnosis with family members. Should a change be made?*

If the members of the practice agree that early CRC screening should be offered to those with a family history of CRC, it follows that patients with CRC should be encouraged to discuss their diagnosis with family members, together with its implications for early screening of family members.

Methods to accomplish the task of informing family members are unresolved. Geneticists often send a letter to the patient, encouraging him/her to share the information with family members. The practice could potentially aid in this effort by producing a fact sheet about CRC risk and screening, for distribution to family members. The outcome of such efforts has not been studied.

In addition, while an argument for early screening of relatives can be made, many questions remain concerning the prevention approach. These questions can serve as the basis for seminar discussions, focused on (1) the extent to which each question is supported by current evidence and (2) what additional studies would best answer the unresolved questions. They include:

1. Is the natural history of colorectal cancer the same in people with and without a family history of colorectal cancer?

2.  Can data from average-risk populations over age 50 be used to predict screening test performance when screening is begun at age 40 in people with a positive family history?

3.  What is the net benefit, in reduced morbidity and mortality, from early screening of people with positive family history?

4.  How should family history data be obtained? Is cancer in more distant relatives important?

5.  Should additional measures be promoted for people with an increased risk of colorectal cancer – e.g., lifestyle risk factors; folate supplementation?

6.  If family history is used to predict risk, will false reassurance and decreased screening occur among people without a family history of colorectal cancer?

7.  How does a strong family history and thus increased risk impact the performance characteristics of differing screening strategies that are now variously recommended?

For further information, see Potter (1999) for discussion of epidemiology of colorectal cancer risk and Winawer et al. (1997) for detailed discussion of colorectal cancer screening.

**CASE # 2**

A resident presents a new patient, referred by the gastroenterology service. She is a 28-year-old woman who recently underwent a subtotal colectomy for right-sided colorectal cancer. Her presenting symptom was lightheadedness secondary to anemia, which is now corrected. The tumor was contained within the wall of the bowel and no additional cancer therapy was recommended. She is otherwise in good health. She is scheduled for annual surveillance of the rectal stump.

**Question for Discussion:**

1.      What additional information do you request from the resident?

**CASE #2 – Discussion**

*1.        What additional information do you request from the resident?*

By virtue of her very early age of onset, this patient is likely to have an inherited predisposition to colorectal cancer, now manifested in her diagnosis.   Presumably she does not have FAP, because no description of multiple polyps (>100) was noted in the GI referral, but this point should be confirmed.  With FAP ruled out, the most likely diagnosis is HNPCC.  Genetic testing may be indicated, and consideration of additional surveillance, e.g. for endometrial cancer, may be indicated.  In addition, family members are at risk for HNPCC, and may benefit from intensive colorectal cancer screening.

**Genetic testing**

HNPCC is associated with mutations in five genes (MSH2, MLH1, MSH6, PMS 1, PMS2), all involving DNA repair functions known as "mis-match repair" – that is, genes that code for proteins involved in repairing DNA replication errors that occur during cell division. Testing is currently available for mutations in MSH2 and MLH1, which account for the majority of identifiable mutations responsible for HNPCC.  Genetic testing within a family can distinguish those who may benefit from early and intensive colorectal screening from those who have not inherited the familial cancer predisposition.  This risk information may also be helpful in making other life decisions.

An important caveat about genetic testing for HNPCC is limited sensitivity – mutations cannot be found in all affected families. Therefore, the optimal testing strategy is as follows:

1.  Test one or more affected relatives
2.  If a mutation is identified, testing can be offered to unaffected individuals, to determine whether they have inherited the mutation and therefore the cancer predisposition
3.  If no mutation is identified in an affected individual, then the testing for that family is deemed "uninformative."  In that case, all at-risk individuals in the family need to continue

screening appropriate to high risk individuals, because testing cannot determine who has inherited a predisposition to cancer and who has not.

**Why test an affected relative first?**

If a mutation cannot be identified in an affected family member, further testing will be non-informative and should not be pursued. However, if a mutation can be identified in an affected relative, both negative and positive test results will be informative in unaffected family members.

**Counseling**

Genetic testing involves potential risks as well as benefits. Knowledge of an inherited predisposition may cause anxiety and family distress, and may also pose a risk of stigmatization and discrimination in access to insurance or employment (Hudson et al. 1995, Rothenberg 1995). Appropriate protection of privacy must be considered. There is expert consensus that individuals contemplating genetic testing should have pre-test counseling, to ensure the opportunity to consider these issues carefully prior to making a decision, and post-test counseling, to ensure that the results are understood (Geller et al. 1997). However, few studies have assessed the efficacy of genetic counseling, and the scope of personal and social risks posed by genetic testing has not been studied systematically.

**Cancer screening in HNPCC**

For people who do not have colorectal cancer:

"People with a family history of colorectal cancer in multiple close relatives and across generations, especially if cancer occurs at a young age, should receive genetic counseling and consider genetic testing for hereditary nonpolyposis colon cancer (HNPCC). They should be offered an examination of the entire colon every 1-2 years starting between the ages of 20 and 30 years and every year after age 40 years" (Winawer et al. 1997).

**RATIONALE**

- High lifetime risk of colorectal cancer, and increased proportion of proximal tumors, in people from families meeting the pedigree criteria suggestive of HNPCC

- Risk increased by age 21

- Genetic tests positive in only about 60%-70% of families

- Some observational data suggest a shortened polyp to cancer interval in HNPCC

**Endometrial cancer screening**

An expert panel recommends endometrial cancer screening for women with HNPCC, on the basis of expert opinion (Burke et al. 1997). The rationale is the high lifetime risk of endometrial cancer (estimated to be ~ 40%), high sensitivity of available screening tests, and excellent clinical outcome when treatment is instituted early. Suggested screening methods include transvaginal ultrasound and endometrial sampling.

**Table 1.**
**Genetics of Colorectal Cancer: Prevalence and Risk**

| Genetic Category | Estimated Prevalence | Estimated Lifetime Risk of Colorectal Cancer | Other Increased Cancer Risks |
|---|---|---|---|
| No family history of CRC | 9/10 | 4-6% | |
| Affected first degree relative | 1/10 | 8-12% | |
| HNPCC | 1/200-1/800 | 80% | Endometrial cancer (estimated lifetime risk of ~ 40%); ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumors) |
| FAP | 1/8000 | close to 100% | Stomach & small bowel |

**Table 2.**
**Inherited Colorectal Cancer Syndromes**

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**Familial adenomatous polyposis (FAP):**

Prevalence:  1/8000
Mode of inheritance: Autosomal dominant
Accounts for ~ 1% of CRC cases
Lifetime CRC risk:  Close to 100%, mean onset age 40
Diagnosis:  >20 (usually >100) colorectal polyps, detectable at puberty or in early adulthood by sigmoidoscopy or colonoscopy (sigmoidoscopy is usually sufficient to make the diagnosis)
Treatment of choice (based on expert opinion and limited observational data): subtotal colectomy (leaving the rectum intact) followed by periodic sigmoidoscopy to evaluate the rectal area for evidence of cancer
Genetic testing: A test for mutations in the APC gene is positive in about 80%-85% of families with FAP

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**Hereditary nonpolyposis colon cancer (HNPCC):**

Prevalence: 1/200 - 1/800
Mode of inheritance: Autosomal dominant
Accounts for ~ 5% of CRC cases
Lifetime CRC risk about 80%, mean onset age 44.   Lifetime risk of endometrial cancer about 40%; other reported cancers in HNPCC families include ovarian and cancers o f the ureter/renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumors)
Recommended screening (based on expert opinion and limited observational data): colonoscopy starting in the 20s; endometrial screening (with ultrasound or endometrial aspirate) in affected females
Genetic testing:  HNPCC is caused by mutations in 5 genes, MLH1, MSH2, PMS1, PMS2, and MSH6.  Testing is available for mutations in MLH1 and MSH2, which account for the majority of identifiable mutations. The overall estimate of sensitivity for such testing in HNPCC is approximately 60-70%.

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# Congenital Hearing Loss

A resident asks...

Why would a primary care physician want to know about the genetics of hearing loss?

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Key Points:

- Newborn screening for hearing loss is being implemented in many states.

- Genetic causes are an important contributor to congenital hearing loss and may have implications for risk to future children.

- Discussions with families about genetic testing need to be sensitive to varying cultural attitudes toward deafness.

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Learning Objectives for the Congenital Hearing Loss Module

Participants will be able to:

- Understand how newborn hearing screening leads to consideration of genetic etiologies

- Identify common genetic causes of congenital hearing loss

- Recognize cultural differences regarding deafness in the deaf and medical communities

**CASE #1**

The resident is seeing a newborn, Scott, and his parents, Laura and Jim W.  Scott's sister, a 3 year old, has received well child care in your office since she was born.   The W's tell the resident that Scott was referred for further evaluation of his hearing -   "after he failed his hearing test," the father adds with some sarcasm.  They want to know what the test was, and "who ordered it in the first place?"  They also want to know what will happen as a result of the referral.

**Questions for Discussion:**

1.  Why is routine newborn hearing screening done?
2.  What factors put a newborn at high risk for hearing loss?
3.  What type of testing is done?
4.  What are the controversies associated with newborn hearing screening?
5.  What is the role of informed consent in the screening process?
6.  What is the usual follow-up after a newborn screening test indicates hearing loss?

**CASE #1 – Discussion**

*1. Why is routine newborn hearing screening done?*

Routine newborn screening is done to detect hearing loss in early infancy, in order to ensure appropriate interventions for language development. Moderate to profound hearing loss in early infancy has been shown to be associated with impaired language development as auditory stimuli during this period is critical to development of speech and language skills. If newborn hearing loss detected on screening is confirmed by definitive diagnosis, then both general therapy and specific treatment based on the etiology of the hearing loss (conductive, sensorineural, or mixed) can be instituted.

Hearing is considered normal if an individual's thresholds are within 15 decibels (dB) of normal thresholds. Hearing loss is categorized by the time period of speech development at which it occurred (prelingual or postlingual); the portion of the hearing system affected (conductive, sensorineural, or mixed) and the degree of loss. Hearing loss is graded as mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90dB), and profound (90dB). Moderate to profound hearing loss is estimated to occur in approximately 1 out of every 2000 newborns.

For all types of hearing loss, early interventions with speech and hearing therapy are considered key components. The most common type of hearing loss found in neonates is sensorineural. Treatment for this depends on the severity of the loss. Amplification through hearing aids is used in the majority of cases; cochlear implantation is a possibility for profoundly deaf children. Nonrandomized, prospective studies have demonstrated superior communication performance in children with prelingually deafness who received cochlear implants as compared to similar children using more traditional tactile or acoustic hearing aids. Language development can also be fostered in profoundly deaf children through American Sign Language (ASL).

*2. What factors put a newborn at high risk for hearing loss?*

Neonates are at a higher risk for sensorineural hearing impairment if they have one of the following factors: family history of hearing impairment, congenital or central nervous system infections, ototoxic drug exposure, prematurity, congenital malformations of the head and neck, trauma, and other factors that have led to an admission to an intensive care nursery.

*3. What are the controversies associated with newborn hearing screening?*

Currently, approximately 35 % of newborns are being screened for hearing loss before hospital discharge according to HRSA reports. The **American Academy of Pediatrics (AAP)** has defined a minimum of five criteria that must be met to justify universal screening. They are:

1. An easy-to-use test that possesses a high degree of sensitivity and specificity to minimize referral for additional assessment is available.
2. The condition being screened for is otherwise not detectable by clinical parameters.
3. Interventions are available to correct the conditions detected by screening.
4. Early screening, detection, and intervention result in improved outcome.
5. The screening program is documented to be in an acceptable cost-effective range

Believing these criteria to be met, the AAP now recommends universal newborn hearing screening. Screening is also recommended by the **American Academy of Audiology**, and **Directors of Speech and Hearing Programs** in State health and welfare agencies, consistent with a 1993 **National Institutes of Health** consensus conference recommending that all infants be screened before hospital discharge. The **Canadian Task Force on the Periodic Health Examination** recommends regular assessment of hearing during well-baby visits during the first 2 years of life using parental questioning and the clap test. However, the **US Preventive Services Task Force** (USPSTF) concludes that there is "insufficient evidence to recommend for or against routine

screening of asymptotic neonates for hearing impairment using evoked oto-acoustic emission (EOE) testing or auditory brainstem response (ABR)." The American Academy of Family Physicians (AAFP) and the USPSTF recommend screening high-risk infants for hearing impairment. The latter two groups are in a process of reviewing their recommendations for scheduled updates.

Arguments made against testing include: 1) the high false positive rate of testing in the face of the low prevalence of disease; 2) the undocumented efficacy of the interventions and 3) concerns by members of the deaf community on the ethics of considering deafness a disability.

**Accuracy of screening tests**

When you are testing *all* newborns for a disease with a relatively low incidence, even an accurate test can result in a high false positive rate (the percentage of newborns diagnosed with hearing loss when they do not have it.) The type of testing done, as well as background noise in the newborn nursery, and operator skill, also affect the testing results. Because the testing, while often mandated by the state, is performed by individual hospitals, current results vary. Well run, established programs can achieve a false positive rate as low as 3%. New programs, those with insufficient training or tracking of results, or those with significant staff turnover can have false positive rates as high as 20%.

**Effectiveness of intervention**

The US Preventive Services Task Force notes that, "while the benefits of various treatments for hearing loss seem manifest, no controlled clinical trials have evaluated the effect of early screening on long-term functional and quality-of-life outcomes. Rather, studies of treatment efficacy are generally observational and retrospective, consisting of clinical series or case-control studies of highly selected patients, often with heterogeneous causes of hearing loss, and incompletely defined treatment regimens or protocols of uncertain compliance." They also note that there has been insufficient study of factors that may influence testing such as patient characteristics (e.g., race or ethnic

group, socioeconomic status, level and laterality of hearing loss, the presence of co-
morbidity, or developmental delay), family characteristics, and the presence and nature of
other therapeutic interventions.

Additionally, there may not be provisions such as financial support to guarantee access to
the suggested interventions for all newborns identified with hearing loss; the
interventions can only be effective if they can be implemented.  Historically, this
parallels the early experience with neonatal phenylketonuria (PKU) screening programs.
PKU is an inherited condition affecting one in 12,000 newborns.  Those affected lack the
ability to metabolize phenylalanine; accumulation of phenylalanine in the tissues of the
brain results in severe mental retardation.  A special diet, including a formula providing
phenylalanine-restricted protein, must be maintained at least through adolescence and
possibly life long to prevent mental retardation.  When the screening process was begun
in the 1960's, some newborns identified with this condition remained untreated due to a
lack of programs for financial support for those unable to afford the special diet.

**Deaf culture**

Many members of the deaf community suggest there is an inherent and unwarranted bias
in the medical profession that views deafness as a disability or as needing medical
intervention.  Rather, they view the deaf community as a separate and valued culture in
which members are bilingual (communicating in both ASL and English).  While this
perspective may be more common in parents who are deaf, the view is held in some cases
by hearing parents as well.  The decision about how to proceed with the evaluation and
potential "treatment" of deafness is a personal family matter for the 90% of deaf children
who are born to hearing parents as well as those born to deaf parents.

*4.  What type of testing is done?*

Because of their age and development, newborns need a testing method that does not rely
on their participation.  Currently, auditory brainstem response (ABR) and evoked
otoacoustic emissions (EOAE) are used, either alone or in combination.  Auditory

brainstem response testing (ABR) measures the electroencephalographic waves generated in response to clicks via three electrodes pasted to the infant's scalp. ABR screening requires the infant to be in a quiet state, but it is not affected by middle or external ear debris. Sensitivity rates have been reported to be 97-100% and specificity rates to be 86-96% in comparison with behavioral testing measures. Despite being the most accurate method, ABR (or modified ABR) is generally not used for a universal *screening* test because of the need for costly equipment and trained operators in all settings.

Evoked otoacoustic emission (EOE) measures sound waves generated by normal cochlear hair cells and detectable with a microphone in the external auditory canal. Using a cutoff of 30 dB to designate hearing impairment, EOE testing has an overall agreement rate with ABR of 91%, with a sensitivity of 84% and specificity of 92%. EOAE may be affected by debris or fluid in the external and middle ear, resulting in referral rates of 5% to 20% when screening is performed during the first 24 hours after birth.
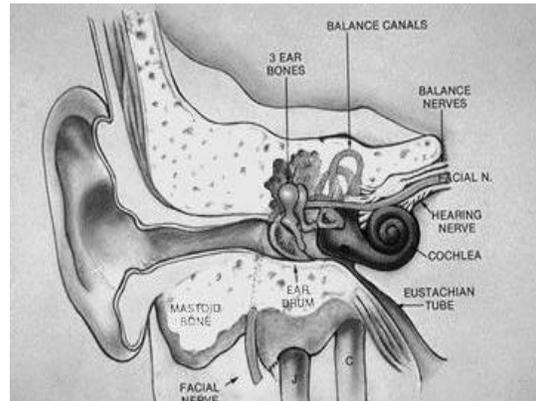
Under the best circumstances, referral rates <4% are generally seen with EOAE combined with automated ABR in a two-step screening system or with automated ABR alone. In a two-step system using EOAE as the first step, referral rates of 5% to 20% for repeat screening with ABR or EOAE may be expected. The second screening may be performed before discharge or on an outpatient basis within 1 month of age. It is recommended by many groups that the screening should be conducted before discharge from the hospital whenever possible.

5. *What is the role of informed consent in the screening process?*

The **Institute of Medicine Committee Report on Assessing Genetic Risks** defines informed consent as: "a process of education and the opportunity to have questions answered – not merely the signing of a form. The patient should be given information about the risks, benefits, efficacy, and alternatives to testing; information about the severity, potential variability, and treatability of the disorder bring tested for; information

about the subsequent decisions that will be likely if the test is positive; and information about any potential conflicts of interest of the person or institution offering the testing." A formalized informed consent process is used routinely in medicine for procedures, surgical interventions, immunizations, experimental medical regimens such as high-risk chemotherapy, etc. Routine medical care often employs an embedded or implied consent process with differing degrees of shared decision making. An informed consent process is not generally used for other well-established newborn screening programs such as neonatal screening for PKU. The appropriateness of adopting this approach to newborn hearing screening, where there are cultural objections to its implication, needs further thought and discussion. **Table 1** lists different state newborn hearing screening programs and the role of parental informed consent in those programs.

**Table 1: Newborn Hearing Screening Legislation in the United States**

| States | Year passed | Full implementation by: | Requires screening of: | Advisory committee established | Covered benefit of health insurance | Report to state DOH | Provision of educational materials? | Informed consent by parents? | Liability immunity? | Religious objection exclusion? |
|---|---|---|---|---|---|---|---|---|---|---|
| Arkansas | 1999 | July 1, 2000 | Hospitals >50 births | Yes | Medicaid | Yes | Yes | | | Yes |
| California | 1998 | Dec. 31, 2002 | Acute care hospitals with CCS funding | Yes | Medicaid | Yes | Yes | Yes | Yes | Yes |
| Colorado | 1997 | July 1, 1999 | 85% of newborns | Yes | | Yes | Yes | | | |
| Connecticut | 1999 | July 1, 2001 | All babies | | | Yes | Yes | | | Yes |
| Georgia | 1999 | July 1, 2001 | 95% of newborns | Yes | | Yes | | | | |
| Hawaii | 1990 | N/A | All babies | | | | | | | |
| Illinois | 1999 | Dec 31, 2002 | All babies | Yes | | Yes | Yes | | | Yes |
| Indiana | 1999 | July 1, 2000 | All babies | Yes | Yes | | | | | Yes |
| Kansas | 1999 | Not Specified | All babies | | | Yes | Yes | Yes | | Yes |
| Louisiana | 1999 | July 1, 2000* | All babies | Yes | | | | | | |
| Maryland | 1999 | July 1, 2000 | All babies | Yes | Yes | | | | | |
| Mass. | 1998 | Not Specified | All babies | Yes | Yes | | Yes | | | Yes |
| Mississippi | 1997 | Jan. 1, 1998 | All babies | Yes | | | | | Yes | |
| Missouri | 1999 | Jan. 1, 2002 | All babies | Yes | Yes | Yes | Yes | | | Yes |
| New York | 1999 | April 1, 2000 | All babies | | Yes | Yes | | | | |
| North Carolina | 1999 | Not Specified | All babies | | | Yes | | | | |
| Oregon | 1999 | July 1, 2000 | Hospitals >200 births | Yes | | Yes | Yes | | | Yes |
| Rhode Island | 1992 | N/A | All babies | Yes | Yes | | | | | Yes |
| Texas | 1999 | April 1, 2001 | Hospitals >100 births | | Yes | Yes | Yes | Yes | Yes | |
| Utah | 1998 | July 1, 1999 | All babies | Yes | | Yes | | Yes | | |
| Virginia | 1998 | July 1, 2000 | All babies | Yes | | Yes | Yes | | | Yes |
| West Virginia | 1998 | July 1, 2000 | All babies | Yes | Yes | Yes | Yes | | | Yes |
| Wisconsin | 1999 | July 1, 2003 | 88% newborns | | | | | | | |
| Wyoming | 1999 | July 1, 1999 | All Babies | | | | | Yes | | |

*6. What the usual follow-up after a newborn screening test indicates hearing loss?*

Upon referral, the neonate undergoes evaluation by a multidisciplinary team experienced in the evaluation of neonatal deafness. Hearing loss is categorized by the portion of the hearing system affected (conductive, sensorineural, or mixed); whether it is primarily due to a genetic cause or environmental one (hereditary or acquired), and if genetic, whether or not it is a component of a genetic syndrome (syndromic or non-syndromic).

The incidence of congenital hereditary hearing impairment is 1:2000 neonates. Of these neonates, 70% have non-syndromic hearing loss. 75-80% of cases of non-syndromic hearing loss are due to autosomal recessive genetic conditions, and of these, 50% are due to DFNB1 mutations. DFNB1 related hearing loss has approximate prevalence in the general population of 14/100,000 (~1/7,000).

Other causes of congenital severe-to-profound hearing loss that should be considered in children who represent isolated (or sporadic) cases in their family are CMV (cytomegalovirus, the most common cause of congenital, non-hereditary hearing loss), prematurity, low birth weight, low APGAR scores, infection, and any illness requiring care in a neonatal intensive care unit.

Physical examination focuses on findings associated with syndromic forms of hearing loss, including the presence of retinitis pigmentosa (Usher syndrome), thyroid enlargement (Pendred syndrome), cardiac conduction defects (Jervell and Lange-Nielsen syndrome), and pigmentary abnormalities (Waardenburg syndrome). (See **Tables 2 and 3**).

**Table 2**

**Selected syndromes inherited in an autosomal recessive manner (in decreasing frequency)**

| Syndrome | Frequency | Hearing loss | Associated findings | Gene(s) involved | Genetic testing available |
|----------|-----------|--------------|---------------------|------------------|---------------------------|
| Usher | most common AR | sensorineural | retinitis pigmentosa | | research only |
| Pendred | 2nd most common | Abnl bony labyrinth | Euthyroid goiter at puberty; vestibular sx | *PDS* gene (chrom locus 7q22-q31) | clinical |
| Jervell and Lange-Nielsen | 3rd most common | | syncopal episodes and sudden death (prolonged QTc) | | high risk families |
| Refsum disease | rare | sensorineural | retinitis pigmentosa; faulty phytanic acid metabolism | | clinical |

**Table 3**

**Selected syndromes inherited in an autosomal dominant manner (in decreasing frequency)**

| Syndrome | Frequency | Hearing loss | Associated findings | Gene(s) involved | Genetic testing available |
|----------|-----------|--------------|---------------------|------------------|---------------------------|
| Waardenburg | most common AD | sensorineural | pigmentary abnormalities; +/- limb abnml., Hirshsprung | *PAX3*, *MITF*, *EDNRB*, *EDN3*, *SOX10* | clinical |
| Branchiootorenal | 2nd most common | conductive, sensorineural, or mixed | branchial cleft cysts or fistulae, malformations of the external ear including preauricular pits, and renal anomalies. | *EYA1* gene in 30% | clinical |
| Stickler | | sensorineural | cleft palate, and spondyloepiphyseal dysplasia resulting in osteoarthritis | STL1, STL2, and STL3. | clinical |
| Neurofibromatosis II | rare | 2nd to bilateral vestibular schwannomas | flat dysplastic tumors or subcutaneous spherical nodules of the peripheral nerves on the limbs and trunk at risk for a variety of other tumors including meningiomas, astrocytomas, ependymomas, and meningioangiomatosis | NF2 | clinical |

**CASE #2**

Return visit of CASE #1, 7 months later

Scott was diagnosed with a hearing loss associated with a DNFB1 mutation.  He has been doing well with speech and hearing therapy.  The family is considering cochlear implants for him.  They want to discuss with you what they have learned from the subspecialists they have seen and have questions about whether or not they should get prenatal testing with their next pregnancy.

**Questions for Discussion:**

1.  What is DNFB1 (connexin 26) related hearing loss?
2.  What is the role of genetic testing?

**CASE #2 – Discussion**

*1. What is DNFB1 (connexin 26) related hearing loss?*

DFNB1 related hearing loss is characterized by congenital (present at birth), non-progressive sensorineural hearing impairment. Usually, the hearing impairment is severe or severe-to-profound; however it can range from mild to severe in different families and within a family.  Except for the hearing impairment, affected individuals are healthy and enjoy a normal life span. Vestibular function is normal; affected infants and young children do not experience balance problems and learn to sit and walk at age-appropriate times.

DFNB1 related hearing loss is suspected in patients who have (1) congenital, non-progressive sensorineural hearing impairment that is mild-to-profound by auditory brainstem response testing (ABR) or pure tone audiometry; (2) no related systemic findings identified by medical history or physical examination.  They may also have a family history consistent with autosomal recessive inheritance of hearing loss (for example, an affected sibling).  However, the majority of people with autosomal recessive diseases represent the first known case in their family.  The diagnosis of DFNB1 related hearing loss is confirmed if the patient has recognized disease-causing mutations in the gene *GJB2* (chromosome 13q11-12) that alters the connexin 26 (Cx26) protein. DNA-based testing of the *GJB2* gene detects about 95% of disease-causing mutations. The most common mutation, 35delG, is found in over two-thirds of persons with DFNB1. About 30% of patients with DFNB1 have other identifiable disease-causing mutations in *GJB2*; at least 21 other disease-causing mutations have been identified.   Available methods of screening for Cx26 mutations have failed to identify disease-causing mutations in some families in whom the diagnosis of DFNB1 has been established by linkage studies; thus, failure to detect a Cx26 mutation does not exclude the diagnosis of DFNB1 (see **GeneClinics** summary for further information).

*2. What are the reasons for doing genetic testing?*

It is important to ascertain and address the questions and concerns of the family/individual when considering genetic testing. Families often want to know the cause of their child's hearing loss. Finding out that it is a genetic cause can often prove comforting, both because of the certainty of a diagnosis is preferred over uncertainty and because it may relieve guilt - "Was it something I (we) did during the pregnancy that caused this?" Conversely, some individuals feel more guilt knowing that the child's condition was inherited from them. The diagnosis of a DNFB1 mutation implies that the child will have a normal life span. It does not differentiate how this child would fare with a cochlear implant as compared to individuals with other sensorineural causes of profound hearing loss.

In addition, a genetic diagnosis may have implications for reproductive decision-making. Prenatal testing is available for couples at 25% risk of having a child with DFNB1 and in whom the disease-causing mutations are known. DNA extracted from cells obtained from amniocentesis at 16-18 weeks' gestation or chorionic villus sampling (CVS) at 9-11 weeks' gestation can be analyzed. In this way, the genetic potential for hearing loss can be diagnosed in utero. Parents may also wish to consider the risk for a child with hearing loss in deciding whether or not to have more children. Genetic counseling, a process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions, can assist families in determining the role of genetic testing or knowledge of genetic risk in their lives.

Carrier detection may be relevant in the reproductive counseling of other relatives of an affected individual. DNA-based testing can only be considered if a disease-causing mutation has been identified in an affected family member. Subsequently, the relatives at risk to be gene carriers can be tested using the same laboratory techniques.

Many deaf individuals are interested in obtaining information about the underlying etiology of their hearing loss rather than information about reproductive risks as they do not consider themselves to be handicapped but define themselves as part of a distinct culture with its own language, customs, and beliefs.  Genetic testing may thus sometimes serve as an explanation for etiology rather than as a factor in reproductive decision-making.

**Follow-up:** After genetic counseling, and reflection over time by the W. family, they decided not to get prenatal counseling with their next child because "they couldn't imagine deciding not to have another child like Scott."  The perceived burden of hearing loss may differ widely across families.  The role of the provider in counseling about prenatal genetic testing is to assure that the families understand the legitimacy of their choices.

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# Dementia

A resident asks...

Why would a primary care physician want to know about the genetics of dementia?

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**Key Points:**

- Genetic contributors to dementia include low penetrance and high penetrance mutations.

- A generic variant of apolipoprotein E (ApoE4) is a low penetrance mutation associated with an increased likelihood of Alzheimer's disease. A significant range of opinions exists regarding testing in these cases. Some experts have suggested testing for ApoE4 as part of the work-up of dementia. However, several expert panels have recommended *against* ApoE testing as a means to detect risk in asymptomatic people.

- In rare families, an autosomal dominant inheritance of early onset Alzheimer's disease occurs, due to high penetrance mutations. Genetic testing *may* be helpful in such families.

- Social implications of genetic testing for AD are significant.

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Learning Objectives for the Dementia Module

Participants will be able to:

- Understand the clinical and social implications of ApoE testing.

- Recognize the family history indicators of autosomal dominant inheritance of early-onset dementia

- Consider the counseling implications for family members considering genetic testing.

**Web Resources for Genetics of Dementia:**

GeneClinics: http://www.geneclinics.org

GeneTests: http://www.genetests.org

**CASE #1**

*Admission:*

You are attending for an inpatient team. The team admitted an 80-year-old woman with acute confusion who is found by labs done in the ER to have a UTI. She improves slightly on antibiotic therapy but continues to be somewhat confused. A more complete history is obtained from her son who reports that she has been failing for some years, with progressive confusion and inability to manage her own affairs. A mini-mental status exam indicates dementia. The resident has found no focal abnormalities on neurologic exam except for mildly impaired hearing bilaterally. After confirmation of these physical exam findings, further work-up is discussed. The team orders a lab work-up to include basic blood chemistries, CBC, thyroid studies, liver function tests, and folate and vitamin B12 levels, and a head CT to rule out structural abnormalities.

**Question for Discussion:**

1. Should any additional etiologies be considered in this patient's work-up?

*Second visit:*

The patient's UTI resolves with treatment. She is discharged home and returns with a caretaker to see the resident in continuity clinic a week later. Lab and CT studies are negative. The resident has found out that the patient's father, an immigrant from Sweden, also developed Alzheimer's Disease (AD) at age 78. On the basis of an article in the New England Journal of Medicine (Mayeux et al. 1998), the resident has ordered an ApoE test. He did so in part because the family history suggests a genetic etiology and in part because the presence of a an ApoE4 allele will increase the likelihood that the patient's dementia is due to AD, while its absence will make AD less likely. You find out at this visit that the test results are available and that Mrs. P is homozygous for ApoE4.

**Questions for Discussion:**

2. How will the ApoE test result change work-up or management?

3. What are the risks and benefits of the ApoE test for Mrs. P?

*Third visit:*

Mrs. P is accompanied by her son for follow-up. The results of the work-up are discussed with Mrs. P's son. After the ApoE4 test result is explained as a finding consistent with a genetic predisposition to AD, Mr. P asks whether this test indicates that he too will get AD.

**Questions for Discussion:**

4. On the basis of Mrs. P's test results, what is Mr. P's risk of AD?

5. What are the risks and benefits of an ApoE test for Mr. P?

6. Does the interpretation of risks and benefits differ by ethnicity?

**CASE #1 – Discussion**

*1. Should any additional etiologies be considered in this patient's work-up?*

The initial work-up focused appropriately on treatable causes of dementia. Other common causes of dementia that should be considered include exposure to drugs or toxins and cerebrovascular disease. In addition to dementia, depression and delirium need to be considered (Ramsdell et al. 1990). Delirium may be caused by factors such as drug reactions, metabolic disorders, systemic illnesses (e.g. infection), cerebrovascular diseases and other CNS disease. Some neurological diagnoses, such as ALS and Parkinson's disease, present with dementia in combination with other focal neurological findings. Alzheimer's Disease (AD) accounts for about half of isolated dementia cases, with most of the remainder due to cerebrovascular disease. [Disclaimer: Experts may disagree about the menu of tests to be ordered in the initial work-up. Some would argue against a routine CT scan. The tests used in this case represent a common approach to work-up for treatable causes of dementia.]

*2. How will the ApoE test result change work-up or management?*

The ApoE4 result will not change work-up or management.

Three common variants of apolipoprotein E (ApoE) occur: ApoE2, ApoE3, and ApoE4. Epidemiological studies have documented ApoE4 as a risk factor for AD (see **Table 1**). ApoE2 appears to reduce risk.

In patients with suspected AD, the presence of one or more ApoE4 alleles has been shown to increase the specificity of the diagnosis in studies of white populations (Mayeux & Schupf 1995; Tsuang et al. 1999). Thus, knowing Mrs. P's ApoE4 genotype increases the probability of that her dementia is due to AD. The positive and negative predictive values of the ApoE4 testing (for the presence of one or more ApoE4 alleles) are estimated to be 88% and 40% respectively (Tsuang et al. 1999). These predictive values are not sufficiently high either to rule in or to rule out AD as a cause of the patient's dementia, and thus would not change work-up. In other

words, an ApoE4 homozygous genotype is not diagnostic for AD, and therefore does not remove the need to rule out causes of dementia, particularly those that are treatable.

There is no proven therapy for AD. Some studies suggest short-term benefit with tacrine, but this therapy remains controversial (Qizibash et al. 1998). The effect of ApoE status on response to tacrine has been evaluated in a few small studies with conflicting results (Rigaud et al. 2000; MacGowan, Wilcock & Scott 1998; Farlow et al. 1998). Thus, there is no scientific basis for determining management on the basis of ApoE status.

*3. What are the risks and benefits of the ApoE test for Mrs. P?*

Potential risks of the ApoE4 test result have to do with labeling: One could postulate that Mrs. P might experience anxiety or other adverse psychological effects as a result of knowing that she has a genetic susceptibility to AD. While these potential effects are likely to be of limited concern in a patient diagnosed with dementia, the patient's relatives could be quite troubled by their own risk for inheriting the disease susceptibility. The benefits to Mrs. P are likewise unclear.

*4. On the basis of Mrs. P's test results, what is Mr. P's risk of Alzheimer's Disease?*

Mr. P has an increased risk of AD. His risk is increased on the basis of his family history alone (see **Table 1**). In addition, he has an increased risk on the basis of his ApoE genotype (see **Table 2**). We know that he must have at least one copy of the ApoE4 allele, because his mother is homozygous for ApoE4. When family history and ApoE4 status are taken together, his risk to develop AD is at least 2 to 3 times higher than average. He also has a higher risk to develop AD before age 65 (see **Table 2**). His risk of developing AD by age 90 is estimated to be 61% (see **Table 3**).

*5. What are the risks and benefits of an ApoE test for Mr. P?*

It is not clear that this risk information provides any benefit to Mr. P.   His mother's ApoE does not allow him to anticipate with certainty whether he will develop AD and, if so, at what age. There is no treatment available to carriers of ApoE4 alleles to prevent AD.

The risk information could cause harm, in the form of anxiety, stigmatization or discrimination. For example, if Mr. P were seeking a promotion and his employer knew of his increased risk for AD, that information could conceivably influence the promotion decision.  Knowledge of an increased risk of AD could also make it harder for Mr. P to obtain life insurance or individually rated health insurance.  These possibilities underscore the concerns many policymakers have expressed about the importance of preserving the confidentiality of predictive genetic information and preventing insurers and employers from using it (Hudson et al. 1995; Lapham, Kozma & Weiss 1996).

*6. Does the interpretation of risks and benefits differ by ethnicity?*

Only one study of ApoE4 status as a predictor of AD risk found no association for African-Americans or Hispanics (Tang et al. 1998).  Another study found ApoE4 to be more predictive in whites than in Hispanics or African-Americans (Devi et al. 1999).

**CASE # 2**

Mr. Y comes to clinic with his wife to discuss an upsetting experience that occurred a week ago. Mr. Y is a 45-year-old computer engineer who manages a software development unit at a large company. He is well known within the industry as the developer of key components of several widely used programs. He had been under a great deal of stress at work, so he and his wife decided to take a vacation. They went to San Francisco to visit friends and attend the opera. On the first day of their trip, their 22-year-old daughter, Sue, who was at home, received a call from Mr. Y. He was in a telephone booth in Union Square. He could not remember what hotel he and Mrs. Y were staying at; he didn't know what to do. Sue gave him the name of the hotel and instructed him to take a taxi back. Shaken, he and his wife returned home. He denies drug use of any kind, drinks moderately, and recently underwent routine medical testing as part of an annual physical, with all results normal. He jogs 30 minutes a day.

Physical exam is unremarkable. There are no focal neurological signs. He is unable to remember three objects. He knows his name and telephone number but has trouble with his birthday, his address and the name of the President. Asked to describe the details of what happened in San Francisco, he says, "The same thing happened to my mother." Prompted, he tells a story that is difficult to follow, about his mother getting lost. Mrs. Y explains that Mr. Y's mother, aged 65, has been in a nursing home for the past 5 years, with a diagnosis of Alzheimer Disease. She also notes that Mr. P has been under considerable pressure at work, with his performance having been described by his boss as unsatisfactory and characterized by faulty management decisions.

**Questions for Discussion:**

1.      How does the family history affect the patient's work-up?
2.      What additional family history would be of value?
3.      What options can be offered to the family?

**Case # 2 – Discussion**

*1. How does the family history affect the patient's work-up?*

Mr. Y requires a careful work-up for neurological and systemic illness, with attention to treatable causes of his recent onset of cognitive difficulties, particularly given his age and previous good health. However, his family history raises the possibility of an inherited early onset AD. Approximately 10% of AD can be accounted for on the basis of mutations with high penetrance that cause an autosomal dominant early onset AD. The majority of these cases are due to mutations in the PSEN1 gene; mutations in two other genes, APP and PSEN2, have also been implicated (see **GeneClinics** review: http://www.geneclinics.org).

*2. What additional family history would be of value?*

A careful three-generation family history would be helpful in determining the likelihood of autosomal dominant early onset AD in Mr. Y's family.

This family history would reveal that Mr. Y's mother was diagnosed with AD at age 60, after at least 10 years of progressive memory problems. In addition, one of Mr. Y's two maternal uncles was noted to have memory problems before he died in an automobile accident at age 48. Mr. Y's maternal grandfather was institutionalized at age 52 and died at age 59; he was said to have "severe mental problems." This grandfather had a sister with memory problems, another sister who died at 72 without evidence of memory problems, and a brother who remained healthy and alert until age 90.

This family history is consistent with autosomal dominant inheritance of early onset AD in several respects:
1. Disease occurs in sequential generations.
2. Both males and females are affected.
3. In each generation, approximately equal numbers are affected and unaffected.

*3.   What options can be offered to the family?*

Mr. Y in fact had early onset AD. His diagnosis and his family history confirm an autosomal dominant AD.  The family may benefit from genetic counseling, to review autosomal dominant inheritance and to learn about options for genetic testing.  Mr. and Mrs. Y have three children, aged 22, 20 and 17, each of whom has a 50% chance to inherit the condition.  Genetic testing is available only for mutations in the PSEN1 and APP genes.  These mutations have nearly 100% penetrance - that is, almost all people with a mutation develop early onset dementia.  The age of onset is usually in the 40's or early 50's although onset in the 30's and early 60's has been reported. Onset after age 65 is thought to be very rare, with penetrance essentially complete by that age. However, testing for PSEN1 and APP mutations is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals (see **GeneClinics** and **GeneTests** reviews).

If Mr. Y were tested and found to have an identifiable mutation in the PSEN1 gene, testing could be offered to his adult children to determine whether they have inherited the predisposition to early onset AD.  This option may or may not be of interest to different family members, and discussion of the implications of testing may be very difficult for the family.   In addition to supervising the evaluation for Mr. Y, his primary care provider may play a crucial role in ensuring that family members' needs for information, counseling and emotional support are addressed over time.

**Table 1**
**Risk of AD with Positive Family History**

| Risk assessed | Definition of "positive family history" | Odds Ratio (95% Confidence Interval) for positive family history versus negative |
|---|---|---|
| AD before age 65, in people with no ApoE4 allele (van Duijn 1994) | Report by at least two family members of first degree relative with dementia, | 2.9 (1.6-5.6) |
| AD in HMO population (Jarvik 1996) | Report by subject or surrogate of parent or sibling with progressive memory problems interfering with daily activities | 2.7 (1.8-4) |
| AD after age 85 (Payami 1997) | Report by subject or surrogate of parent or sibling with AD, dementia or progressive memory loss | 3.8 (0.87-16.5) |

**Table 2**
**Risk of AD or Dementia According to ApoE Genotype**

| Risk assessed | Ethnicity | Odds Ratio (95% Confidence Interval) for: | | |
| | | 1 or 2 ApoE4 alleles | 1 ApoE4 allele | 2 ApoE4 alleles |
| --- | --- | --- | --- | --- |
| AD before age 65 **AND** positive family history (van Duijn) | White (Netherlands) | 3.3 (1.6-7.0) | 2.6 (1.2-5.7) | 7.9 (1.7-36.0) |
| AD before age 65 **AND** negative family history (van Duijn) | White (Netherlands) | 1.9 (1.0-3.7) | 1.6(0.8-3.2) | 4.9 (1.3-19.9) |
| AD after age 65 (Evans 1997) | Predominantly white (Boston) | 2.3 (1.1-4.9)* | | |
| AD after age 65 (Tang 1998) | White (New York) | 2.5 (1.1-6.4)* | | |
| AD in HMO population **AND** positive family history (Jarvik 1996) | White (Seattle) | | 5.0 (2-11)** | 12.0 (3-59) |
| AD in HMO population **AND** negative family history (Jarvik 1996) | White (Seattle) | | 2.3 (1.4-4)** | No controls identified |
| Dementia after age 85 **AND** positive family history (Payami 1997) | White (Oregon) | 9.13 (1.74-47.8) | | |
| Dementia after age 85 **AND** negative family history (Payami 1997) | White (Oregon) | 4.34 (0.99-1.04) | | |

\* ApoE4/ApoE2 excluded from analysis
\** ApoE3/ApoE4 only

**Table 3**
**Lifetime Risk of AD in People with a Family History of AD**
**According to ApoE Genotype of Affected Relative (Martinez et al. 1998)**

| ApoE4 Genotype of Proband | Risk of AD by age 90 in First Degree Relative |
|---|---|
| ApoE4/ApoE4 | 61% |
| ApoE4/ApoE4 *or* ApoE4/ApoE3 | 50% |
| ApoE4/ApoE3 | 46% |
| ApoE3/ApoE3 | 29% |

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# Developmental Delay

A resident asks…

    Why would a primary care doctor want to know about the genetics of developmental delay?

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**Key Points:**

- Genetic causes may account for 5%-25% of children with developmental delay, including some children with normal physical exam or minimal physical findings.

- Although a specific diagnosis rarely leads to curative treatment, it can inform the family about a child's prognosis and enable the child to receive needed services.

- In some cases, a genetic diagnosis of developmental delay informs the family about risk to other family members.

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Learning Objectives for the Developmental Delay Module

Participants will be able to:

1. Understand the role of genetics in work-up of a child with developmental delay.
2. Review fragile X syndrome.
3. Review velocardiofacial syndrome.

**CASE # 1**

This case demonstrates the evaluation and work-up of a child with developmental delay who is ultimately found to have Fragile X syndrome.

**Presentation:**

A continuity clinic resident presents Chad, a two-year-old child who has come for well child care. Chad's last well child visit was at 15 months of age. At that time the history and physical were normal, but Chad had no expressive language development. A decision was made to wait and watch his development in this arena. Subsequently, Chad has been seen for three episodes of otitis media. The current history indicates that Chad still has no expressive language development. He appears to hear normally and will follow simple commands. His gross and fine motor development appear normal for age. Socially, the child is described as very shy. Parents note that he is not friendly with other children or adults and consistently avoids eye contact. He is frequently irritable and is physically quite active at home.

**PMH:** Chad was the 3.5 kg product of a normal pregnancy and delivery. Mother does not relate a history of prenatal illness, medications, alcohol use or substance abuse. Chad's APGAR scores were 8 at one minute and 9 at five minutes and his neonatal course was notable only for a peak bilirubin of 17 on day 4 of life. Subsequently he has been healthy with the exception of 6 episodes of otitis media to date. Chad's newborn screen results for PKU, sickle cell anemia, and hypothroidism were normal.

**Additional history obtained with directed questioning:**

**FH:** Chad has a healthy 4-year-old female sibling, Kara. Kara also is shy but has been doing well in a day care environment. Kara began to speak at about 15 months of age. Chad's mother, Monica, is 26 years old and in good general health. She has a history of depression and an anxiety disorder but is currently not in therapy or receiving medication. Monica was the youngest of three children, with an older brother and a sister. Her brother had a history of being "slow" in school. He was killed in an auto accident when Monica was an adolescent. Her sister left home at 16 years of age and has had only intermittent contact with Monica over the years.

She is healthy, married, but has no children to Monica's knowledge.  Monica's parents are in reasonable health for their age; at age 66, her father has hypertension and degenerative joint disease and at age 60, her mother has diet-controlled diabetes.   Chad's father, Jack, is healthy.  Monica is pregnant at 12 weeks gestation.

**SH:**  The family is of modest means.  Monica works in environmental services at a downtown office building.  She struggled in school, attaining only a 10th grade education.  Jack works as a backhoe operator in a local construction company.  He also struggled in school but completed his high school degree.  Monica and Jack are happily married and there is no history of alcohol or substance abuse or domestic violence.  The family's health insurance is covered by Medicaid, although Jack will soon be eligible for coverage through his employer.  Monica and Jack are practicing Catholics.

**PE:**  Chad is at the 20th percentile in weight, 30th percentile in height and 95th percentile in head size – these measures are consistent with previous points on the growth chart.  He is withdrawn in the mother's lap and resistant to physical exam.    Consistent with previous exams, he is morphologically normal. The only notable finding is serous otitis media bilaterally.  In addition, he has a long face and prominent ears; he looks like his mother in this regard.  His skin findings are normal, without café-au-lait spots, shagreen patches or hypopigmented spots.

**Questions for Discussion:**
1.  What diagnostic considerations should be considered with this presentation?
2.  Was the right decision made at 15 months?
3.  How can physical exam contribute to evaluation of the patient?
4.  How would a pedigree or genogram help to evaluate the family?
5.  What work-up (if any) would you recommend that the resident pursue?
6.  What is the value of a specific diagnosis for the family?

**Case # 1 – Discussion**

*1. What diagnostic considerations should be considered with this presentation?*

Developmental delay is a common problem encountered in pediatrics practice, and a genetic etiology is an important consideration. Genetic causes are currently estimated to account for 5%- 25% of children with developmental delay, and include both rare and relatively common disorders (Curry et al. 1997). This is a rough estimate because most studies have been done in clinical or institutional settings where selection biases may occur, and older studies may have missed genetic causes that are now identifiable. Some associated physical findings and co-morbidities may increase the likelihood of a genetic cause of developmental delay – e.g. congenital malformations, hearing impairment (see the **Congenital Hearing Loss** module in this manual), growth retardation. However, some genetic causes, including chromosomal microdeletions, may be associated with a normal examination or mildly abnormal physical findings that are difficult to differentiate from the normal range. Genetic studies that may help in the evaluation of a child with developmental delay include chromosomal studies to evaluate conditions such as trisomies and chromosomal deletions, specific diagnostic tests such as those for Fragile X, and evaluation for metabolic disorders. Because there are many potential genetic tests to consider in this setting, some of them costly, follow up over time, with a stepwise approach to diagnosis, is appropriate when history and physical exam findings are normal or non-specific. When testing is considered, a genetic approach may help to direct testing to those conditions most likely to be present.

In this case, persistent developmental delay has been observed and it is appropriate to proceed to additional work-up. There is little in the presenting history to narrow the differential. The prenatal and birth history help to rule out prenatal and perinatal causes, such as teratogenic agents, prematurity, significant birth asphyxia, congenital infections, and exposure to toxins (tobacco, alcohol, or other medications or substances that may be abused during pregnancy). The general categories to be considered include idiopathic or familial mental retardation without a specific defined cause, environmental causes (such as family stress, domestic violence, child

abuse or neglect), chromosomal disorders, metabolic disorders, and single gene disorders, including X-linked developmental delay, which is an important consideration in affected males. Other possibilities include Pervasive Developmental Delay (and Asperger's Syndrome, which involves impaired social interaction, often with repetitive and stereotypical patterns of behavior in a child with a normal IQ; see http://www.udel.edu/bkirby/asperger/ for more information), mild congenital or acquired hearing loss, and history of illness associated with an increased risk of mental retardation, such as episodes of dehydration/acidosis; failure to thrive; or chronic illnesses such as congenital heart disease. Occasionally, a child brought up in a non-English speaking family, might be shy and not interact fully with English speaking professionals. Thus a good professional interpreter is necessary. In addition to these non-genetic possibilities, a genetic etiology should be considered in a child with developmental delay where the pregnancy and perinatal history offer no indicators of the cause.

In considering causes of developmental delay, additional history is often crucial. Past medical history may provide important indicators of cause – e.g. morbidities associated with specific syndromes. A family history of learning problems, psychiatric disorders, autism or mental retardation increases the likelihood of an inherited cause (see question 4 below). Social history may help to identify environmental causes of learning difficulties or may point to behavioral problems that contribute to making a diagnosis.

2. *Was the right decision made at 15 months?*

In retrospect, indicators for additional work-up were present at 15 months, including language delay and a family history of learning difficulties. The timing for pursuing additional work-up is always a matter of judgment, but some physicians would have considered additional work-up at the earlier visit.

*3. How can physical exam contribute to the evaluation of the patient?*

Physical exam findings are an important clue to further work-up. All children with developmental delay should have a complete examination, to identify physical anomalies that may indicate a specific syndrome or increase the index of suspicion for a chromosomal disorder. When physical anomalies are present, consultation with a dysmorphologist may help to define the possibilities and best testing options. A dysmorphologist can help to determine whether subtle physical findings are worthy of work-up, and may provide useful advice about specific syndromes to consider, based on a constellation of physical findings. Any facial, skeletal or limb asymmetry is usually associated with a genetic etiology. Genetic problems are also more common when there is a discrepancy in the anthropomorphic measurements over time. In this case Chad's height and weight were generally in the 20-30th %tile, while his head circumference was in the 95th %tile. Congenital hearing loss in combination with development delay may also suggest specific syndromes (see **Congenital Hearing Loss** module). Skin findings may be important, as indicators of conditions such as neurofibromatosis Type 1 or tuberous sclerosis.

*4. How would a pedigree or genogram help to evaluate the family?*

A pedigree provides a visual summary of the family structure; if relevant health problems are noted, the pedigree allows a quick assessment for patterns suggestive of inherited disease. When considering developmental delay, a family history of a psychiatric problem, learning disabilities and/or mental retardation in more than one family member is suggestive of a genetic cause. In this case, the family history of learning problems in the child's maternal uncle raises the question of X-linked mental retardation, an important cause of developmental delay in males, and in particular the diagnosis of **Fragile X syndrome**. Approximately 40% of X-linked mental retardation is due to Fragile X syndrome. The mother's learning difficulties would also be compatible with this possibility, because about half of Fragile X carriers have learning problems.

This pedigree information points to the importance of assessing Chad for physical findings compatible with a known X-linked disorder, such as Fragile X syndrome. At the child's current

age of age 21 months, the physical characteristics of Fragile X may not be apparent, but would include large head, long face, prominent forehead, large ears, prominent jaw.  After puberty, large testes are observed.

A genogram includes information about social as well as biological relationships (McGoldrick et al. 1999).  Considering Chad's family, it is worth noting that both his parents had learning problems and that his mother has a history of anxiety and depression.  These factors could contribute to a poor learning environment at home; Chad's mother's anxiety and depression could have produced emotional or social problems that contributed to Chad's developmental delay.

*5.  What work-up (if any) would you recommend that the resident pursue?*

Taking family history, developmental history and physical exam into account, Fragile X is a possibility, and should be tested for (see **GeneClinics** http://www.geneclinics.org and **GeneTests** http://www.genetests.org for details of testing).

*6.  What is the value of a specific diagnosis for the family?*

A specific diagnosis has several potential benefits.  In this case, a diagnosis of Fragile X provides an explanation for the child's developmental delay, and provides the family with prognostic information.  Answering the "why" is often a value in and of itself when a child has developmental delay.  In addition, services that may be of benefit to the child, for both cognitive and social needs, may be easier to obtain with a specific diagnosis.  The diagnosis also provides information about other family members who may be at risk for this condition, including future children, and thus leads to consideration of additional genetic testing in the family.

The developmental delay seen in Fragile X syndrome is typically moderate rather than severe.  Often the phenotype includes behavioral problems such hyperactivity, poor eye contact and withdrawn social behavior, perseverative speech, and at the extreme, autism.  The prevalence of

Fragile X has been estimated to be about 1 in 5000; among unselected males with developmental delay the condition is estimated to be present in 3-6%.

The molecular genetics of fragile X are complex (see **GeneClinics** summary; McIntosh et al. 2000). The phenotype of developmental delay is determined primarily by the number of CGG trinucleotide repeats in the gene: a "full" mutation is said to be present when >230 repeats are present, and is associated with developmental delay in 100% of males and approximately 50% of females. The normal number of CGG repeats is <55; when an intermediate number are present (55-230), a "premutation" is said to be present. People carrying a premutation generally have normal intellect (rare cases of mild impairment have been reported). However, when a premutation is transmitted by the mother, it may expand to a full mutation (see **GeneClinics** in the **Reference** section of this manual for table summarizing the empiric risk for an affected child when a mother carries a premutation). Additional molecular genetic complexity derives from modifying factors: aberrant gene methylation and CGG repeats. Rarely, reversions may occur (reduction in the number of CGG repeats with gene transmission from parent to child). In addition, about 1% of patients with Fragile X syndrome have a different molecular defect in the gene. These complexities underscore the importance of detailed counseling and careful consideration of testing options when testing is undertaken.

The diagnosis of Fragile X has important implications for the family, and may well correct previous misapprehensions about the significance of the condition. For instance, it is not uncommon for children with Fragile X syndrome to display symptoms that may lead to a mis-diagnosis of idiopathic autism or another disorder having substantially different implications. In this case, it is the likely explanation of the mother's learning difficulties and those of her deceased brother. The recurrence risk is high for this family. Although testing will be needed to confirm the mother's status, her son's status suggests that she carries the full Fragile X mutation. Prenatal diagnosis and termination of affected pregnancies are options in this situation, but may not be of interest to the family. Supportive counseling over time may help the parents to take in all the implications of the Fragile X diagnosis. These include both reproductive issues and the question of sharing the diagnosis and its implications with other family members.

**CASE # 2**

This case illustrates the slow unfolding of the diagnosis of **22q11deletion syndrome**. The diagnosis was not made on the initial genetics evaluation, but was ultimately made at age 32.

Cathy was born in 1968 with a cleft palate and a single umbilical artery. She was diagnosed with cerebral palsy, with no known birth trauma. The mother subsequently had a normal pregnancy, Cathy's younger sister Brenda, and then a miscarriage of a fetus with a cleft palate. The family was offered genetic consultation but initially did not pursue it because they planned no more pregnancies. At age 4, Cathy, who had always been somewhat "slow," had difficulty adjusting to a day care environment, and presented for further evaluation. Standardized testing indicated that cognitive development was mildly to moderately delayed, motor development was mildly delayed, and language development was significantly delayed.

Her medical history at the time of her evaluation at age 4 was otherwise unremarkable. Physical exam revealed evidence of cleft lip and palate repair but no other craniofacial abnormalities. Growth had been consistently at the 30%, with normal head circumference. She had no abnormal skin findings. She had a mild gait abnormality consistent with the diagnosis of CP. Work-up included a chromosomal study and metabolic studies, both of which were normal. The family was counseled that no specific genetic etiology could be found. She was considered to have CP and mild to moderate MR of unknown, presumably multfactorial etiology.

Cathy continued to have learning difficulties but did well with them and completed high school. Her big problems began as a young adult when she developed a picture of intermittent psychosis, thought to be temporal lobe epilepsy. She has had at least 2 grand mal seizures as well. A psychiatrist followed her for years and tried virtually every seizure and antipsychotic medicine with intermittent relief at best but steady deterioration. A neurologist followed her as well. She developed fairly severe sleep apnea but was unable to tolerate any treatment including O2. Although these medical problems were of increasing concern, no further etiological investigation was pursued for many years, because the complete evaluation done at age 4 had revealed nothing

*Developmental Delay Module: Page 9*

specific. She progressed to the point that she was hospitalized in a psychiatric locked ward, so preoccupied with frightening voices that she was unable to be managed short of an involuntary hospitalization.

When she was 32, her mother got in touch to report that her sister Brenda had talked to a neurologist in Boston who advised re-evaluation. He noted that clinical understanding of developmental problems and their associated complications had progressed considerably since Cathy's initial evaluation at age 4; perhaps a second look might be worthwhile. This conversation triggered an interest in additional work-up. The family did not expect that there would be a treatment but were still seeking an explanation for their daughter's difficulties. Brenda, who was married and thinking of having children, also wondered if Cathy's problems implied any risk for her children. As their family physician, they have brought their questions to you and are asking for your recommendation. What will you say to the family?

**Question for Discussion:**

1. How can genetic evaluation be helpful at this point?

**CASE # 2 – Discussion**

*1.  How can genetic evaluation be helpful at this point?*

As in all areas of medicine, there has been an increasing ability to find specific causes for developmental delay.  Given advancing technology, it is especially important for the primary care physician to think "genetic causes" if there is no clear-cut etiology in a child with developmental delay. The genetic hypothesis is particularly important when there is more than one malformation or deformation or when there is a positive family history.  The psychiatric and cognitive/developmental history are an important part of the family history as well.  In this case there is a clear indication for exploration of the genetic possibilities.

Recognition of new syndromes and technological improvements in testing—in particular, improved cytogenetic techniques—have led to an increasing ability to define specific genetic causes for problems like Cathy's.  Thus, a negative work-up 25 years ago does not preclude a genetic cause to Cathy's problems.  The value of a genetic diagnosis in Cathy's case would be three-fold:  (1) it would provide an explanation; (2) it might provide valuable prognostic or therapeutic information; and (3) it would inform the family about the potential for other family members to be affected, in particular, about any risk to Brenda's children.

The approach to work-up is the same as it would be in an initial evaluation: medical history, full physical exam looking for any dysmorphic features other than the known cleft lip and palate; growth measurements; developmental history, family history, social history.  Testing considerations would include chromosomal studies and biochemical testing.

In Cathy's case, repeat chromosomal studies revealed a 22q11 deletion (**22q11 deletion syndrome**).  This abnormality, due to a small deletion on chromosome 22, would not have been detected in the chromosomal studies done 28 years ago, and illustrates the power of new, more precise testing techniques. The increased sensitivity of the test also has led to a recognition of the wide phenotypic variability of this syndrome.  It is now known to encompass the phenotypes

previously described as diGeorge syndrome and velocardiofacial syndrome. As these associations imply, the phenotypic manifestations are variable (see **GeneClinics** summary in the **Reference** section of this manual). The most common manifestations are cardiac abnormalities, palatal abnormalities, learning disabilities and characteristic facial features. Of these, Cathy had only two: palatal abnormalities and learning disabilities. Her CP and psychiatric problems are assumed to be part of the syndrome, but the frequency with which these complications occur is not yet known. Molecular diagnosis, in this case the documentation of a specific small chromosomal deletion, thus can lead to a re-evaluation of the epidemiology and definition of a syndrome. It is likely that many patients are yet to be identified, who, like Cathy, have somewhat atypical features of the syndrome as currently described.

In addition to providing an explanation for Cathy's problems, this diagnosis led to testing of both parents, to ensure that neither was a deletion carrier (this occurs in about 6% of cases). Both were chromosomally normal, indicating that Cathy carried a de novo mutation. However, the history of miscarriage of a fetus with cleft lip and palate raised the possibility of gonadal mosaicism (i.e. the possibility that the de novo chromosomal deletion in fact occurred in gonadal tissue of one of the parents, and thus could be passed on to subsequent children). For this reason, Brenda was also tested, and was found to be without the deletion. For the family, the most reassuring aspect of Cathy's diagnosis is the knowledge that there was nothing else they should have or could have done to ameliorate Cathy's problems. This knowledge brought a relief that was unexpectedly great; Cathy's parents had not previously realized how much they had worried about possible oversights in Cathy's care.

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# Iron Overload

A resident asks....

Why would a primary care doctor want to know about the genetics of iron overload?

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**Key Points**:

- Iron overload occurs in 1/200 to 1/400 of people. In the average primary care practice, this figure translates to about 4 to 8 patients with iron overload.

- In some patients, iron accumulation is progressive and causes serious complications such as cirrhosis, diabetes, and cardiomyopathy.

- Complications of iron overload can be prevented with phelobotomy (removal of 1-2 units of blood periodically), yet many patients are not diagnosed until organ damage has occurred.

- Early symptoms of iron overload are typically non-specific, and include common symptoms seen in primary care, such as fatigue, joint pain and palpitations.

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Learning Objectives for the Iron Overload Module

Participants will be able to:

- Know the prevalence and clinical implications of iron overload
- Understand the use of serum iron measures in diagnosis of iron overload
- Understand the implications of HFE genotype data in diagnosis of hereditary hemochromatosis
- Understand the counseling and confidentiality issues that arise in family-based detection of people with hereditary hemochromatosis.

**CASE # 1**

A 47-year-old man presents with aching joints and fatigue.  He has had the symptoms for several years.  He has no other health complaints, although he notes some non-specific stomach discomfort on review of systems. He also notes a past history of excess alcohol use. He has seen two other doctors for his joint pain and fatigue.   He has been advised to exercise regularly and take non-steroidal anti-inflammatory medications for his joint symptoms, but these measures have not provided symptomatic relief.  He has not had any chest pain or shortness of breath.  He denies depressive symptoms including anhedonia, low self-esteem, and changes in appetite or sleep patterns.

*Exam findings:*

Exam findings include normal HEENT exam with anicteric sclera, and no facial edema noted; normal thyroid gland.  There is a normal cardiac and lung exam without edema (pitting or non-pitting). Abdominal exam reveals mild hepatomegaly.  Rectal exam is normal, with insufficient stool for guaiac testing.  Neuro/musculoskeletal exam shows normal strength and sensation, normal reflexes and lack of inflammatory joint changes or joint tenderness.  The mental status exam is normal with normal affect. No psychomotor retardation noted.

*Lab work-up:*

Suspecting anemia, possibly due to GI bleeding, his new physician orders stool cards and a hematocrit.  Because of the mild hepatomegaly, he also orders liver function tests.  In addition, he orders a TSH to rule out hypothyroidism.  Stool cards are negative, TSH is 2.0, hematocrit is 45 and AST and ALT are mildly elevated.

**Questions for Discussion:**
1.  Based on the history, what are the diagnostic considerations and how should they be evaluated?
2.   How do the exam findings change the differential?
3.   Based on the lab findings, what are the most likely diagnoses?  What additional testing is indicated?

**CASE #1 - Discussion**

*1. Based on the history, what are the diagnostic considerations and how should they be evaluated?*

The differential for fatigue would include depression, hypothyroidism, anemia (possibly caused by GI bleeding given the history of non-steroidal anti-inflammatory use), CHD or other cardiovascular disease, chronic fatigue syndrome, occult chronic illness (such as liver disease or renal disease) and iron overload (see **Table 1** below). The differential for joint pain would include osteoarthritis, inflammatory arthritis, and iron overload. Additional history may be helpful at this point, including detailed history concerning mood and vegetative signs of depression, specific questions related to GI blood loss, and more information about character and duration of fatigue and joint pain.

**Table 1.**
**Work-up of a patient with fatigue**

| Condition to consider | Prevalence | Risk factors | First step in diagnosis | Positive predictive value | Negative predictive value | Confirmation of diagnosis | Treatment | Evidence for outcome benefit from treatment |
|---|---|---|---|---|---|---|---|---|
| Depression | 3-5% | Young, female, single, divorced, separated, seriously ill, past history or family history of depression | Mental status; history of vegetative signs; various screening instruments available | Average PPV for screening instruments: 84% | Average NPV for screening instruments: 72% | Clinical judgement; exclusion of other causes of fatigue | Anti-depressant therapy | RCT data |
| Hypothyroidism | 1-4% | Female, older age, Downs syndrome | TSH | 89-95% | 90-96% | | Synthetic thyroid replacement | Clinical observation; efficacy of treatment of subclinical hypothyroidism uncertain |
| Anemia | <1% - 10% | Young children, elderly & women of child-bearing age | CBC | | | | Treatment dependent on cause of anemia | Clinical observation |
| Iron overload | 0.3-0.5% | Male, middle age or older, family history of iron overload | TS | 30-40% for TS cut-off of 60 | >95% for TS cut-off of 60 | Repeat TS, serum ferritin, additional measures of iron overload | Phlebotomy | Clinical observation |
| Chronic fatigue syndrome | 0.2-0.4% | Female, middle-aged | Mental status exam, history, & physical | | | Exclusion of other known causes of fatigue | Treat symptoms | Clinical observation |
| Other chronic illness (e.g. liver disease, renal disease) | Variable | | Additional history and exam to focus differential | | | | | |

*2. How do the exam findings change the differential?*

There is no evidence of CHD on exam, which in addition to a negative history of related complaints argues against this as an etiology. Nothing on exam suggests hypothyroidism, but a negative exam does not rule it out. Negative joint exam reduces the likelihood of inflammatory arthritis. Hepatomegaly increases the likelihood of occult liver disease, although the physical exam is not very accurate.

*3. Based on the lab findings, what are the most likely diagnoses? What additional testing is indicated?*

The presence of mild elevations of liver function tests raise additional diagnostic possibilities, including chronic hepatitis, hepatic drug reaction, alcoholism, and rarer conditions such as autoimmune hepatitis. Other lab tests rule out hypothyroidism and anemia. Iron overload remains a consideration.

**CASE # 2**

A resident presents a patient with a question about hemochromatosis (HHC). The patient is a 30-year-old woman in for a routine Pap test. However, she also wonders whether she should be tested for HHC. She reports that her brother has just been diagnosed with this condition – she is not sure what it is – and is now insisting that everyone in the family be tested. He says there is a genetic test that will determine who is affected. She is skeptical: "he's always overreacting." She reports no symptoms. She has one child, aged 5, who is healthy. Her only medication is an oral contraceptive. A hematocrit 2 years ago was 36.

**Question for Discussion:**

1. What additional information would be helpful in counseling her about a work-up for HHC?

**Additional history:**

The patient's brother arranges to have a letter sent from his doctor. The letter confirms that the brother has iron overload, diagnosed after an episode of atrial fibrillation. He has undergone the removal of 20 units of blood by phlebotomy and now has a serum ferritin <50. His HFE genotype is C282Y/H63D.

**Questions for Discusion:**

2. What is the patient's risk to have HHC?
3. Which testing approach is preferable in determining whether she has HHC – iron studies or testing for HFE mutations?
4. Are there additional considerations for the patient or her family as she considers her testing options?

**CASE # 2 – Discussion**

*1. What additional information would be helpful in counseling her about a work-up for HHC?*

Further information about her brother's reported diagnosis of hemochromatosis would help to determine her risk – e.g., What was the basis of the diagnosis? How was the diagnosis confirmed? If her brother's medical history confirms a diagnosis of HHC, the patient has a 25% chance of having the same HFE genotype as her brother, and therefore a genetic susceptibility to hemochromatosis. Her risk for complications of iron overload would be lower, because clinical observations indicate that penetrance of HFE mutations is less than 100% and is lower in females than males. Nevertheless, her risk for iron overload would be well above that of the population. She might benefit from testing for transferrin saturation, according to the testing pathway outlined below. She is also likely to benefit from additional information about HHC.

**Testing pathway to detect people with increased risk of iron overload, based on serum iron measures:**

1. Check random transferrin saturation (TS = serum iron /TIBC x 100%)
    - For TS < 45% – Iron overload is unlikely. If TS < 16 %, iron deficiency is present
    - For TS 45% to < 60% – Iron overload is possible; given the patient's family history further work-up would be appropriate
    - TS ≥ 60% – Iron overload is more likely; additional work-up is merited

2. If TS is elevated, re-check (fasting if possible) to confirm, and check serum ferritin (SF)
    - If SF is ≥ 200, iron overload is likely. Further work-up for complications of iron overload is indicated; de-ironing (removal of iron by phlebotomy) is indicated. [Note – for men, a higher serum ferritin threshold is generally used – e.g., 300.]
    - Elevated TS levels are found in 1-6% of the population, depending on the cut-off used. Persistently elevated TS is an indicator of significantly increased risk of iron overload if other causes (such as liver disease and iron-loading anemia) are absent. The effect of the

TS cutoff on the detection of affected persons is illustrated in **Table 2** below (based on

Bradley et al. 1996).

**Table 2.**
**Estimates of hemochromatosis detection rates (DR), false positive rates (FPR), and odds of being affected given a positive result (OAPR) according to sex and TS cutoff level.**

| TS Cutoff | Males | | | Females | | |
|---|---|---|---|---|---|---|
| (%) | DR (%) | FPR (%) | OAPR* | DR (%) | FPR (%) | OAPR* |
| 50 | 94 | 6.2 | 1:12 | 82 | 3.3 | 1:8 |
| 55 | 91 | 2.3 | 1:5 | 75 | 1.0 | 1:3 |
| 60 | 86 | 0.7 | 2:3 | 67 | 0.2 | 2:1 |
| 65 | 79 | 0.2 | 2:1 | 58 | <0.1 | >3:1 |
| 70 | 72 | <0.1 | >4:1 | 48 | <0.1 | |

[a] Assumes a prevalence of affected persons of 5 in 1000.

Additional biochemical evidence of iron overload is typically required for the diagnosis of HHC. Usually an elevated serum ferritin and liver function tests (e.g., AST, ALT, alkaline phosphatase and bilirubin) are obtained; if both are abnormal, a liver biopsy may be recommended, to confirm HHC by measurement of the hepatic iron index and to assess for the presence of liver fibrosis or cirrhosis. If the serum ferritin is elevated but liver function tests are normal and no hepatomegaly is present, many experts recommend quantitative phlebotomy: the removal of 1-2 units of blood per week until the serum ferritin reaches a low normal range. Removal of a defined amount of iron (e.g., 3-4gms) by this procedure confirms the diagnosis of HHC.

*2. What is the patient's risk to have hemochromatosis?*

Her brother's medical history confirms HHC. Her risk is to have a hemochromatosis genotype is 25%. Her risk to have complications of iron overload is substantially lower, partly because penetrance is lower in women and partly because her brother's genotype is associated with much lower penetrance than the more common HFE genotype seen in affected patients (C282Y/C282Y), as discussed under question 4 below.

*3. Which testing approach is preferable in determining whether she has hemochromatosis – iron studies or testing for HFE mutations?*

Her brother's HFE genotype is known, so HFE testing can be used to identify other affected siblings. However, it should be noted that the penetrance of the C282Y/H63D genotype is much lower than that of the C282Y/C282Y genotype. This lower penetrance can be inferred from the fact that case control studies demonstrate relatively few cases with this genotype (about 5% of cases - see **Table 2** above), yet this genotype is about four times more common in the population than the C282Y/C282Y genotype. As a rough estimate, the penetrance of the C282Y/H63D genotype is in the 1% range (Burke et al. 2000).

As a result, HFE mutation testing would be a means to identify whether the patient has inherited an increased risk for iron overload, but a positive genetic test result would still be associated with a low risk of iron overload. Serum iron measures (TS, followed by serum ferritin) are a more accurate way to determine whether the patient has iron overload.

In planning work-up and monitoring of the patient, it is important to take into account that iron overload occurs over time. If the patient's serum iron measures are normal now, she may benefit from repeat testing every 2-3 years. The genotype test could be used to determine the value of such a surveillance program, that is, the surveillance program would not be needed if she had a normal HFE genotype. Conversely, a positive genotype test in the setting of normal iron measures could be stigmatizing, or cause the patient to believe herself to be ill, or make her vulnerable to loss of insurance options.

*4. Are there additional considerations for the patient or her family as she considers her testing options?*

Once an individual is diagnosed with iron overload, and the work-up reveals that the cause is HHC, work-up of all biological relatives is appropriate. Family-based detection is an efficient way to detect people with an increased risk of iron overload, but requires careful attention to

patient confidentiality and preferences.  Genetic studies reveal that the relationship between genotype and phenotype is complex.  Two mutations have been shown to be associated with disease, one of which, C282Y, is more severe than the other, H63D.  Iron overload has also been observed in mutation carriers and in people without HFE mutations (see **Table 3** below).

**Table 3.**
**HFE genotypes in patients with iron overload and in control populations**
**Pooled data - studies of people of European descent (Hanson et al. 2001)**

| Genotype | % of Cases | % of Controls |
|---|---|---|
| C282Y/C282Y | 77.5% | 0.4% |
| C292Y/H63D | 5.3% | 1.8% |
| H63D/H63D | 1.5% | 2.0% |
| C282Y/+ | 3.6% | 9.2% |
| H63D/+ | 5.2% | 21.6% |
| +/+ | 6.9% | 65.1% |

Although the genotype-phenotype relationship is complex, most people with HHC carry two *HFE* mutations are present.  An affected person has thus usually inherited an *HFE* mutation from each of his/her parents.  The parents can be either carriers, who are usually without evidence of iron overload, or can be themselves affected.  The most important family history is of disease suggestive of HHC – e.g. primary liver cancer or cirrhosis and diabetes in the same relative; HHC may not always be recognized as the cause of disease in family members.

Siblings of affected persons have a 25% chance of inheriting the same genotype as their affected sibling and thus of having an increased risk of iron overload.   When an affected person marries a carrier, their children each have a 50% chance of inheriting a genotype predisposing to iron overload.  Since about 10% of people in the general population carry the C282Y mutation, children of a person with hemochromatosis have about a 5% chance of inheriting the predisposition to iron overload.  Genetic counseling may help an affected person and his/her family members to understand this inheritance pattern.

As shown in **Table 3**, about 7% of persons with HHC carry no known *HFE* mutations; clinical findings consistent with HHC are also sometimes seen in C282Y and H63D heterozygotes. As a result the value of genetic testing as a means to detect affected family members depends on the genotype of the index case: if the index case has a C282Y/C282Y genotype, testing may be useful and efficient means to detect others at risk in the family. Other HFE genotypes may be less useful for this purpose. Even when genotype data is informative, iron studies are necessary to determine the need for medical management.

Health care providers can facilitate family detection by counseling a patient with HHC about the value of informing family members, by providing letters and information sheets to be passed on to family members, and by making counseling available to family members. In this way, information can be provided about hemochromatosis, the procedures involved in family screening and the potential of screening to identify family members who may benefit from phlebotomy treatment.

The diagnosis of hemochromatosis may have adverse social consequences. Anecdotal reports of discrimination in insurance and employment have been reported after a diagnosis of HHC (Alper et al. 1994). Loss of self-worth or increased concerns about health may occur when a genetic risk state is identified (Markel 1992). The likelihood or scope of these risks is unknown. However, careful attention to the confidentiality of information, and respect for individual preferences regarding testing, are important issues as information is provided to the family about HHC.

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# Ethical, Legal, and Social Implications (ELSI)
# Of Genetic Information

A resident asks...

Why would a primary care doctor want to know about the ethical, legal and social implications (ELSI) of genetic information?

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**Key Points:**

*Genetic information, like other medical information*:

* has the power to help or harm patients and must be considered in making patient care decisions.

* is complex, and communication of risks and uncertainties must be attended to thoughtfully and critically.

* will arise in your practice. It is helpful to think through how you will respond in the face of inevitable questions, some of them involving difficult judgments.

*In addition, genetic information, unlike much of medicine*:

* provides information about family members and relatives. Disclosure of family information can often be helpful to family members but also can lead to breaches of confidentiality that must be considered and addressed proactively.

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Learning Objectives for the Ethical, Legal, and Social Implications (ELSI) Module

Participants will be able to:

* Recognize that ELSI issues are integrated into, not separate from, all medical care.

* Know that family members are affected by genetic testing and screening decisions.

* Understand how disease labels can help some patients and cause psychological harm for others.

* Know that while ELSI issues are highlighted in genetic cases, similar issues are present throughout medicine. Physicians can draw on their expertise in primary care practice in addressing genetics issues and, conversely, bring an awareness to primary care that is heightened by working with genetic cases.

**CASE #1**

Mrs. M seeks advice about getting BRCA1 gene test. She is 45 years old and generally healthy. Her mother, Mrs. G, was diagnosed with ovarian cancer last year.  As part of a research study, the mother was found to carry a BRCA1 mutation conferring increased risk for breast and ovarian cancer. The mother's sister (the patient's maternal aunt) died of breast cancer at age 48 and in retrospect is assumed to have had the same BRCA1 mutation.

The patient's sister has now undergone testing and found that she also carries the BRCA1 mutation; she is considering prophylactic oophorectomy and mastectomy, and she has urged her sister to be tested.  Mrs. M is uneasy about being tested. She wonders if there is an alternative.

The resident is not sure what to say.  After discussing the case with you, the resident goes back in the room and asks the patient more about her concerns re: testing.  Mrs. M states that she thinks a positive test result will make her think about cancer all the time. She is also worried about losing her health insurance.  Mrs. M states that she is healthy, has mammograms annually and performs breast self-exams regularly.  She had a hysterectomy last year for dysfunctional uterine bleeding.  Her surgery was performed about a month after her mother's diagnosis and, because of the diagnosis and the patient's age, her ovaries were removed as well.  She is a little shocked that her sister's doctor suggested prophylactic mastectomy and that her sister is considering it.  She states that she is not interested in a prophylactic mastectomy.

**Question for Discussion:**

1. What are the pros and cons of testing for Mrs. M?

**CASE # 1 - Discussion**

*1. What are the pros and cons of testing for Mrs. M?*

The pros and cons of testing are strongly influenced by Mrs. M's preferences and expectations. For this reason, it is important for the resident to explore with Mrs. M her thinking about the testing. This discussion also helps to identify additional information the patient may need to make a decision about testing. It is important that the resident creates an atmosphere in which the patient can honestly assess her reasoning and associated emotions. It is also important the resident not convey that there is a **right** decision for this question.

There are two potential benefits of testing. If the test is negative in the face of her mother's positive test (a 50% chance), Mrs. M may have the relief of knowing she has not inherited the high cancer risk present in her family. If the test is positive, Mrs. M might benefit from more aggressive prevention strategies. She has clearly rejected prophylactic mastectomy but might consider tamoxifen or other yet to be identified interventions (see the **Breast Cancer Module** for more discussion of her prevention options). For example, she might be a candidate for research trials such as a current multi-center study on MRI screening for high risk women. The patient might benefit from more information about such possibilities (including the information that they could be pursued without testing). As to harms, Mrs. M has already articulated a major harm of testing: she perceives that a positive test result would lead to breast cancer worry. While the 50% chance of a negative test might offer relief, she still may not choose to be tested, given her concern about a positive test result. Mrs. M's concern also speaks to the issue of labeling.

Labeling can occur in both genetic and non-genetic diagnoses. While being identified as at risk for a disease is not the same as being diagnosed with the disease, the effect of the risk label on an individual's self-perception could be similar. The individual might start thinking of herself as a "genetic time bomb" and wonder when, rather than if, the disease will occur. The individual might view herself as a "mutant," or not "normal." Knowing that she has a genetic predisposition might make her more likely to pursue other risk reduction strategies more actively. Or, it might make her feel that disease is inevitable and that other risk reduction is

worthless.   Others (friends, family members, physicians) might also have different expectations of the individual given her risk status.  This kind of effect has been seen in patients with elevated cholesterol, who sometimes think of themselves has having heart disease rather than a risk for it. Some studies suggest that when the risk predictor is genetic the condition may be viewed as being more likely and less susceptible to modification.

Anxiety and depression are also potential reactions to labeling, whether genetic or non-genetic. As Mrs. M's concern suggests, one cannot assume that because no disease condition has been diagnosed – only some degree of future risk – there is reduced worry.  Another, less obvious, negative psychological reactions is survivor guilt on the part of individuals in a family who test negative for a deleterious mutation and feel guilty, responsible and unsure of how to act in regard to their own good fortune and their relative's misfortune.

Mrs. M has also expressed concern about losing her health insurance.  If she receives health insurance through a large group plan based on her or her husband's employer (as most Americans do), she is unlikely to lose her health insurance as the result of a genetic test. However, this concern cannot be routinely dismissed.  Genetic information, like other risk information, is potentially of interest to insurers providing individually rated or small group plans.  Many states have passed legislation intending to prevent the use of genetic test results, and efforts to create federal legislation are also on-going, reflecting a societal consensus that characterizes such practice as unfair discrimination. (However, few laws prevent insurers' use of family history information in individual rating.)  These laws have not yet been tested in the courts, and the potential for health insurance discrimination remains problematic for those having individual or small business health insurance (a minority of the insureds).  Genetic information may also be of interest to life and disability insurers; few state laws address the use of genetic information for these insurance products.

In summary, Mrs. M has expressed two important personal arguments against testing: concerns that a positive test result will increase her worry and that it will potentially threaten her health insurance.  Equally important, she has already had an oophorectomy and is uninterested in a prophylactic mastectomy.  All other available risk reduction strategies – including aggressive

breast cancer screening and consideration of tamoxifen – are available to her without genetic testing.

For women in Mrs. M's situation, testing is an option but not an "indicated" procedure. In Mrs. M's case, she has made it clear that she does not want testing. The most important goal of the counseling discussion is to ensure that she has considered all aspects of the testing opportunity to her satisfaction in making this decision.

**CASE #2**

A resident presents a 35-year-old man with a 5-year history of intermittent abdominal pain consistent with irritable bowel syndrome.  In the course of a full examination, small testes are noted.  On questioning, the patient notes low sex-drive. Initial work-up reveals a low testosterone level; further work-up includes a chromosomal study that indicates the patient has a 47,XXY karyotype (Klinefelter's).  He has an appointment to discuss his results.

He teaches mathematics in middle school.  He lives with his wife and son.

**Questions for Discussion:**
1. What advice would you give the resident to help in the discussion of the diagnosis with the patient?
2. What are the benefits and burdens of labeling to consider?

**CASE # 2 - Discussion**

*1. What advice would you give the resident to help in the discussion of the diagnosis with the patient?*

As the resident discusses the diagnosis, he is doing more than informing the patient of a medical condition and the appropriate treatment. All diagnoses carry with them other social, cultural and psychological meanings as filtered thorough the patient's viewpoint and health model. The resident must simultaneously assess the medical information to be conveyed, the patient's baseline perspective and comprehension of the new information, the psychosocial implications of the diagnosis for the patient, and the support systems the patient has. The visit should attempt to establish or continue a strong patient-doctor relationship, because the patient's understanding is likely to be an ongoing process that cannot be addressed in one visit.

While the diagnosis is new, the patient has had this condition all his life. If the diagnosis feels overwhelming, it may be helpful for the patient to put the diagnosis in that context. Patients often go through different phases of reaction and incorporation of new diagnoses; what is positive to the patient at one stage may become negative at another. Over time, the resident can help the patient gain a perspective on his disease.

For many patients, the idea of a genetic diagnosis often has powerful associations with inferiority. Patients may feel shame or guilt upon hearing a genetic diagnosis, and self-stigmatization can occur. This concern is often raised in the context of genetics, but may be of equal concern when a non-genetic diagnosis is made – e.g. cancer, diabetes or HIV. In this case, a patient with the diagnosis of Klinefelter's might wonder if he is "not truly a man." On the other hand, providing a diagnosis for previously mysterious signs and symptoms can be very reassuring. Some diagnoses, including Klinefelter's, can indicate the need for specific treatment (in this case, testosterone), or make a patient eligible for certain services and support groups.

*2. What are the benefits and burdens of labeling to consider?*

For this patient, the diagnosis of Klinefelter's syndrome came as a relief. His diminished sex-drive had caused tension in his marriage. The diagnosis provided a basis for treatment with testosterone, which led to improved sex drive and sense of well-being. The diagnosis also led to a social issue with important and sensitive implications. The fact that 95% of people with Klinefelter's are infertile raises doubt about the paternity of his child. However, raising the question of his likely infertility could be painful and disruptive. Further it would be difficult to disprove that he is his son's biological father, short of a formal paternity analysis – a procedure not likely to be in the family's best interests. While it is appropriate for him to know that most men with Klinefelter's syndrome are infertile, further exploration of the topic should perhaps follow the patient's initiative. Like many other conversations between patient and physician, this discussion will benefit from sensitivity and established trust.

Genetic labeling often involves both benefits and burdens (see **Table 1**). The balance between these is often highly subjective.

**Table 1**
**Benefits and Burdens of Disease Labeling**

| Benefit | Burden |
|---|---|
| Understanding | Stigmatization |
| Specific management or prevention options | Discrimination |
| Access to services | Helplessness |

**CASE # 3**

A 35-year-old man is diagnosed with medullary carcinoma of the thyroid and undergoes a successful resection. He has no family history of thyroid cancer, pheochromocytoma or other endocrine abnormalities. He is an only child; his father died at age 32 in an automobile accident, and his mother is in good health at age 67. Given the early age at which his cancer occurred, he is tested for mutations in the RET gene and found to have a mutation associated with Multiple Endocrine Neoplasia Type 2 (MEN2). He is counseled about autosomal dominant inheritance and the risk to future children. He asks whether a child already born would be at risk, because he has a 10–year-old son, with whom he has not been in contact for many years.

Based on the counseling he receives, he calls the mother of his child to let her know of their son's 50% risk to inherit the RET mutation and the recommendation that the child be tested. She tells him she doesn't ever want to hear from him again and hangs up. He notes that they parted under bad circumstances (he was drinking heavily) and asks his primary care provider to contact her to explain the need for follow-up for his son. The resident wants to know how to proceed.

**Questions for Discussion**:

1. Is testing of the patient's son recommended?
2. If so, what role should the resident play in helping this patient get the information to the child's mother?

**CASE # 3 - Discussion**

*1. Is testing of the patient's son recommended?*

The **American Society of Human Genetics -American College of Medical Genetics**
(ASHG/ACMG) recommends against testing children unless there are medical indications:

> "If the medical or psychosocial benefits of a genetic test will not accrue until adulthood,
> as in the case of carrier status or adult-onset diseases, genetic testing generally should be
> deferred…The stigmatization and deleterious effects on self-image are great and should
> only be risked when medical benefit is possible. Although sympathetic to the
> considerable difficulties inherent in living with uncertainty about the health status of the
> child, the Task Force does not feel that these warrant foreclosing the child's right to make
> an independent decision in regard to testing in adulthood."

However, childhood testing is recommended if a genetic test is associated with high penetrance,
the disease may occur during childhood, and there is an intervention to prevent the disease that
must occur during childhood.

This statement of principle is at the center of the ethical issues raised by this case. The stringent
criteria for testing in childhood are met in this case. Medullary carcinoma of the thyroid can
occur in early childhood in MEN2, and prophylactic thyroidectomy is usually recommended by
age 5. Uncontrolled clinical studies support this approach (see **GeneClinics** summary:
http://www.geneclinics.org). For families who are unwilling to consent to phrophylactic
thyroidectomy, periodic screening (for evidence of C-cell hyperplasia) is an alternate approach.
Thus, specific preventive actions are available to monitor a child carrying an MEN2 mutation.

*2. If so, what role should the resident play in helping this patient get the information to the child's mother?*

This question raises the physician's duty to disclose information to a family member. The American Society of Human Genetics has published a position statement on this issue (Knoppers et al. 1998). This document suggests that disclosure should be permissible under exceptional circumstances when:

- attempts to encourage disclosure on the part of the patient have failed
- harm is highly likely, serious, imminent and foreseeable
- at-risk relatives are identifiable
- disease is preventable, or medically accepted standards for treatment or screening are available
- the harm from failing to disclose outweighs the harm from disclosure

(see Knoppers et al. 1998 for detailed discussion of these issues).

When genetic risk is identified, genetic professionals typically encourage family members to share information with others who may benefit from testing. In the case of MEN2, risk to children is usually discussed as part of the initial counseling (as occurred in this case) and follow-up testing is arranged as part of care for the family as a whole. Here, because of the estrangement between the parents, the father cannot participate in ensuring his son's care. However, he has given the provider permission to contact his son's mother to ensure care for his son. This point is important, because current privacy regulations require a patient's explicit permission before medical information is shared. In this circumstance, it is permissible for the provider to contact the mother directly.

Privacy regulations underscore the provider's obligation to maintain the confidentiality of medical information. However, if the information represents a significant, imminent and remediable threat to another's person's health, the provider may need to consider whether s/he has a duty to contact the person at risk (or in the case of a minor, as here, the minor's guardian or legal representative), in the absence of explicit permission. This is similar to cases in which a patient makes a serious threat to injure another identifiable person, in which the provider is

obligated to inform the person at risk (see discussion in Knoppers et al. 1998). Most cases of genetic risk provide less clear-cut evidence of imminent risk. Finding the correct balance between the obligation to disclose and the obligation to maintain patient confidentiality may be difficult, and it may be appropriate to seek legal counsel if this conflict arises.

**CASE #4:**

A resident presents a 42-year-old woman who has come for an annual exam. The resident has performed routine health maintenance, including a pelvic examination with Pap test and a clinician breast exam; a dT booster has been ordered. The patient is a non-smoker, drinks minimal alcohol, and has no known family history of breast, colorectal or ovarian cancer. Her father has heart disease at age 70 and she reports no other family history of concern. She notes that her brother is an alcoholic. Her exam is normal.

The resident is troubled because she has received a phone call from the patient's brother prior to the visit, asking her to work the patient up for Charcot-Marie-Tooth disease (CMT). The brother states that he is worried about his sister because he has seen her stumble many times and thinks she has the disease, which also affects him and their father. He has tried to talk with his sister about it and she has refused to discuss it. He does not want the resident to mention that he has called. He also asks that the resident inform him of the patient's status so that he can take whatever measures are necessary to ensure that she is protected from complications of her neurological disease.

The resident has reviewed information about CMT disease on the **GeneClinics** website. She understands that this is an autosomal dominant disorder resulting in peripheral neuropathy. Thus, the brother's history (if reliable) would indicate that the patient has a 50% risk to inherit the condition. In the absence of physical findings, and with conflicting history from the patient and her brother, the resident is unsure how to proceed.

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**Question for Discussion:**

1. What ELSI concerns are raised by this situation?

**CASE #4 - Discussion**

*1. What ethical concerns are raised by this situation?*

The patient is apparently unaware of her father's and brother's diagnosis. The history from the brother may be unreliable, but CMT would be an unusual diagnosis to provide in a fabricated medical history.

Physicians are obligated to respect the confidentiality of medical information. However, in this case, the resident has obtained information with potential consequences for her patient from an outside source. The provider of the information (the patient's brother) has requested that his call not be disclosed; but his call is not protected by medical confidentiality. As a result, whether or not to disclose the call is a matter of physician discretion. Among the issues the resident should consider are: preserving family relations, whether or not knowing about the call will foster or hinder trust from her patient, and whether the source of the information is especially germane to the case. Will it help or hurt the patient's care or the doctor-patient relationship to disclose the call? On the one hand, disclosing the call could provide the basis for a discussion of CMT and family members who are reported to be affected. This discussion could be helpful in assessing the patient's knowledge and attitudes toward her potential risk. It might also provide further insights about the patient's family. On the other hand, the patient might react with anger to the information that her brother called, and her brother can be expected to feel anger if his call is revealed. At minimum, the information provided by the brother's call should be evaluated for its contribution to the patient's care and well-being.

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# Resources on the World Wide Web

This resource list was prepared by HRSA with input from CDC and NIH for the "3rd National Conference on Genetics and Public Health: Connecting Research, Education, Practice & Community", September 19-20, 2000 in Ann Arbor, Michigan.  This list was last updated on August 17, 2000.

The GPC group has begun to add web resources to this list as they come to our attention and as we find them useful.  We consider this an on-going project and welcome suggestions.

# Genetics and Public Health
# Resources on the World Wide Web

1.      **Genetic Alliance** http://www.geneticalliance.org/
The Genetic Alliance (formerly The Alliance of Genetic Support Groups, Inc.) is an international coalition of individuals, professionals and genetic support organizations that is working together to enhance the lives of everyone impacted by genetic conditions.

2.      **National Human Genome Research Institute** http://www.nhgri.nih.gov/
The National Human Genome Research Institute (NHGRI) was originally established in 1989 as The National Center for Human Genome Research (NCHGR). Its mission is to head the Human Genome Project for the National Institutes of Health (NIH).  NHGRI is one of 24 institutes, centers, or divisions that make up the NIH, the federal government's primary agency for the support of biomedical research.

3.      **National Organization for Rare Disorders** http://www.rarediseases.org/
The National Organization for Rare Disorders (NORD) is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

4.      **Office of Rare Diseases** http://rarediseases.info.nih.gov/ord/index.html
The Office of Rare Diseases (ORD), National Institutes of Health (NIH) provides information on more than 6000 rare diseases, including current research, publications from scientific and medical journals, completed research, ongoing studies, and patient support groups.

5.      **Rare Genetic Diseases In Children** http://mcrcr2.med.nyu.edu/murphp01/homenew.htm
An Internet jump-station to sources of information on rare genetic diseases affecting children. Under the aegis of the NYU Medical Center, this site has provided its services continuously since April 30, 1996.

6.      **Online Mendelian Inheritance in Man** http://www3.ncbi.nlm.nih.gov/Omim/
This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. The database contains textual information, pictures, and reference information. It also contains copious links to NCBI's Entrez database of MEDLINE articles and sequence information.

7. **Kansas University Medical Center** http://www.kumc.edu/gec/geneinfo.html
Information for genetic professionals at the University of Kansas Medical Center is updated regularly with clinical, research, and educational resources for genetic counselors, clinical geneticists, and medical geneticists. This is a useful resource for teachers, as well.

8. **National Institutes of Health** http://www.nih.gov/
Web site for the National Institutes of Health (NIH), U.S. Department of Health and Human Services.

9. **National Cancer Institute** http://cancernet.nci.nih.gov/h_genetics.html
CancerNet is the gateway to the most recent and accurate cancer information from the National Cancer Institute, a component of the National Institutes of Health.

10. **Family Village** http://www.familyvillage.wisc.edu/index.htmlx
The Family Village is a global community that integrates information, resources, and communication opportunities on the Internet for persons with cognitive and other disabilities, for their families, and for those that provide them services and support. The community includes informational resources on specific diagnoses, communication connections, adaptive products and technology, adaptive recreational activities, education, worship, health issues, disability-related media and literature, and much, much more!

11. **The Genetics Resource Center** http://www.pitt.edu/~edugene/resource/
The Genetics Resource Center is an online resource and starting point for genetic-counseling-related information. The web-site is constructed and maintained by the Genetics Education and Counseling Program at the University of Pittsburgh.

12. **National Coalition for Health Professional Education in Genetics**
    http://www.nchpeg.org
Started in 1996 by the American Medical Association, the American Nurses Association, and the National Human Genome Research Institute, the N ational C oalition for H ealth P rofessional E ducation in G enetics (NCHPEG) is a national effort to promote health professional education and access to information about advances in human genetics. NCHPEG members are an interdisciplinary group of leaders from over 100 diverse health professional organizations, consumer and voluntary groups, government agencies, private industry, managed care organizations, and genetics professional societies. By facilitating frequent and open communication between stakeholder groups, NCHPEG seeks to capitalize on the collective expertise and experience of members and to reduce duplication of effort.

13. **The Genome Action Coalition** http://www.tgac.org
The Genome Action Coalition, begun in 1995, is comprised of patient advocacy organizations, professional organizations in the field of genetics and genomics, consumer organizations, university-based research facilities, pharmaceutical research companies and biotechnology companies. The Coalition exists to promote an environment in government and in the private sector in which genome research can continue to flourish.

14.     **The Council for Responsible Genetics** http://www.gene-watch.org/org.html
The Council for Responsible Genetics (CRG), founded in 1983, is a national nonprofit organization of scientists, environmentalists, public health advocates, physicians, lawyers and other concerned citizens. CRG encourages informed public debate about the social, ethical, and environmental implications of new genetic technologies, and advocates for socially responsible use of these technologies. CRG monitors the development of new genetic technologies in two broad program areas: human genetics, and commercial biotechnology and the environment.

15.     American regional networks which provide genetic services to patients and professionals:

**GLaRGG: Great Lakes Regional Genetics Group**
http://www.waisman.wisc.edu/glargg/index.htmlx  Serving: Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin

**MARHGN: Mid-Atlantic Regional Human Genetics Network**
http://www.pitt.edu/~marhgn/ Serving: Delaware, Maryland, New Jersey, Pennsylvania, Virginia, Washington D.C., and West Virginia

**MSRGSN: Mountain States Regional Genetic Services Network**
http://www.mostgene.org Serving: Montana, Wyoming, Utah, Colorado, Arizona, New Mexico

**NERGG: New England Regional Genetics Group**
http://www.acadia.net/nergg/index.html Serving: Maine, Vermont, New Hampshire, Massachusetts, Rhode Island, Connecticut

**Pacific Southwest Regional Genetics Network**   http://www.psrgn.org/ Serving: California, Hawaii and Nevada

**SERGG: Southeastern Regional Genetics Group**
http://www.cc.emory.edu/PEDIATRICS/sergg/ Serving: Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee

**TEXGENE: Texas Genetics Network** http://www.tdh.texas.gov/texgene/texgene.htm
Serving: Texas

**Genetics Network of New York State** http://www.wadsworth.org/index.htm Serving: Puerto Rico, the Virgin Islands and New York State

16.     **HuGEM II Project** http://www.dml.georgetown.edu/hugem
The purpose of the HuGEM II Project is to provide educational training and resources to increase the knowledge of and sensitivity to human genetics, the Human Genome Project, and the ethical, legal, and psychosocial issues of genetic testing and research for members of seven collaborating professional organizations.

17.     **March of Dimes - Resource Center** http://www.modimes.org
The Resource Center provides accurate, timely information and referral services to the public. The staff of the Resource Center includes trained professionals who help people, one on one, to address personal and complex problems. They answer questions from parents, health care providers, students, librarians, government agencies, health departments, social workers--people from all walks of life and from around the world.

18.     **New York Online Access to Health (NOAH)** http://www.noah.cuny.edu/
NOAH:  New York Online Access to Health seeks to provide high quality full-text health information for an underserved population of health consumers that is accurate, timely, relevant and unbiased. NOAH supports English and Spanish.  Originally funded by the U.S. Department of Commerce's National Telecommunications and Information Administration (NTIA) and matching grants, NOAH currently has numerous sponsors including the March of Dimes.

19.     **Human Genome Project Information** http://www.ornl.gov/hgmis/
Learn the basics about the Human Genome Project: what it is; its progress, history, and goals; frequently asked questions; and other information for people new to the project.  Funded by the U.S. Department of Energy.

20.     **Secretary's Advisory Committee on Genetic Testing (SACGT)**
        http://www4.od.nih.gov/oba/sacgt.htm
Secretary of Health and Human Services Donna Shalala chartered the Secretary's Advisory Committee on Genetic Testing (SACGT) in June 1998 in response to recommendations of two working groups commissioned jointly by the National Institutes of Health (NIH) and the Department of Energy (DOE) for the Human Genome Project.

21.     **The National Center for Cultural Competence (NCCC)**
        http://www.dml.georgetown.edu/depts/pediatrics/gucdc/cultural.html
The National Center for Cultural Competence (NCCC) is a component of the Georgetown University Child Development Center, Center for Child Health and Mental Health Policy, and is housed within the Department of Pediatrics of the Georgetown University Medical Center.  The mission of the NCCC is to increase the capacity of health care programs to design, implement and evaluate culturally competent service delivery systems.

22.     **The National Heart, Lung, and Blood Institute (NHLBI)** http://www.nhlbi.nih.gov/
The National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources.

23.     **Centers for Disease Control (CDC)** http://www.cdc.gov/genetics
Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention. The site provides current information on the impact of human genetic research and gene discoveries on disease prevention and health promotion. The site includes a weekly update of news stories, scientific literature, announcements, events, and public health perspectives on advances in human genetics.

24.     **The Human Genome Epidemiology Network (HuGE Net)**
        http://www.cdc.gov/genetics/hugenet/default.htm
A global collaboration of individuals and organizations committed to the development and dissemination of population-based epidemiologic information on the human genome. The site features information on: population-specific prevalence data on human gene variants, epidemiologic data on the association between genetic variation and diseases in different populations; quantitative population-based data on gene-environment interaction; and population impact on the use of genetic tests and services in improving health and preventing disease.

25.     **U.S. Department of Energy (DOE)**
        **The Human Genome Program** http://www.er.doe.gov/production/ober/genome.html
The Human Genome Program was initiated by DOE in 1986 to map and determine the complete DNA sequence of the human genome. The principal goal of this international program is to determine a representative human DNA sequence of all 3 billion base pairs in the human genome. The U.S. Human Genome Project is jointly managed by DOE and the National Institutes of Health (NIH).

        **Joint Genome Institute and Gene Sequencing Facility**
        http://www.er.doe.gov/production/ober/jgipsf.html
The DOE Joint Genome Institute (JGI) is the product of a managerial strategy to use the complementing strengths of DOE labs involved in human genome research and avoid duplication of effort. Formed in 1997, the JGI is a virtual laboratory whose work will be conducted in a number of labs allowing more efficient and effective use of expertise and resources across labs.

26.     **American College of Medical Genetics**
        http://www.faseb.org/genetics/acmg/acmgmenu.htm
The American College of Medical Genetics (ACMG) is an organization composed of biochemical, clinical, cytogenetic, medical and molecular geneticists, genetic counselors and other health care professionals committed to the practice of medical genetics.

27.     **American Society of Human Genetics**
        http://www.faseb.org/genetics/ashg/ashgmenu.htm
The American Society of Human Genetics (ASHG) was established in 1948 to provide leadership in research, education and service in human genetics. Accordingly it elected to publish The American Journal of Human Genetics and sponsor an annual research meeting. The human genetics community grew and spawned a new field of endeavor, genetic counseling, to support delivery of clinical genetics services.  Over 5,000 members include researchers, academicians, clinicians, laboratory practice professionals, genetic counselors, nurses and others involved in human genetics.

28.     **Communities of Color and Genetics Policy Project**
        http://www.sph.umich.edu/genpolicy/
Michigan State University Center for Ethics and Humanities in the Life Sciences and Tuskegee University National Center for Bioethics in Research and Health Care have combined projects to form a five year project designed to provide policy recommendations based on public perceptions and responses to the explosion of genetic information and technology. The project

also tests the process of community dialogue as an effective means to engage citizens in thoughtful and productive discussions about policy needs regarding genetic information and technology and other value-laden issues.

29.     **The Sickle Cell Information Center** http://www.emory.edu/PEDS/SICKLE/
The mission of this site is to provide sickle cell patient and professional education, news, research updates and world wide sickle cell resources. It is the mission of our organizations to provide world class compassionate care, education, counseling, and research for patients with sickle cell disease. It is our mission to help break the sickle cycle.

This Sickle Cell Information Web Site is Sponsored by the following partners: The Georgia Comprehensive Sickle Cell Center at Grady Health System, Atlanta, Georgia; Emory University School of Medicine, Department of Pediatrics, and Department of Medicine, Division of Hematology - Oncology; The Sickle Cell Foundation of Georgia Inc.; Morehouse School of Medicine.

30.     **National Immunization Program** http://www.cdc.gov/nip/
The National Immunization Program (NIP) is a part of the Centers for Disease Control and Prevention, located in Atlanta, Georgia. This site provides recent and accurate immunization information from the NIP, the Federal Government's principal agency for immunization policy and recommendations. You will find a wide range of immunization information including information about vaccine preventable diseases, the benefits of immunization, and the risks of immunization vs. the risk of disease. In addition, you will find a wide range of educational materials and resources.

31.     **National Immunization Program Immunization Registry Clearinghouse - Activities and Updates** http://www.cdc.gov/nip/registry/articupd.html
The National Immunization Program (NIP) of the Centers for Disease Control (CDC), is committed to promoting the development and maintenance of state- and community-based computerized registries which capture immunization information on all children. To aid in the development of these systems, NIP has developed an Immunization Registry Clearinghouse.

**MCHB/HRSA Grantees**
1.     **GeneTests** http://www.genetests.org
Funded by the National Library of Medicine of the NIH and Maternal & Child Health Bureau of HRSA, GeneTests™ is a genetic testing resource that includes: A Genetics Laboratory Directory, a Genetics Clinic Directory, an introduction to genetic counseling and testing concepts (in About Genetic Services), and a Powerpoint slideshow presentation for genetics professionals (in Teaching Tools).

2.     **GeneClinics** http://www.geneclinics.org
A clinical information resource relating genetic testing to the diagnosis, management, and genetic counseling of individuals and families with specific inherited disorders.

3.      **The National Newborn Screening and Genetic Resource Center (NNSGRC)**
http://GENES-R-Us.uthscsa.edu

A cooperative agreement between the Maternal and Child Health Bureau, Genetic Services Branch, HRSA and the University of Texas Health Science Center at San Antonio, Department of Pediatrics.  The mission of the NNSGRC is to provide a forum for interaction between consumers, health care professionals, researchers, organizations, and policy makers in refining and developing public health newborn screening and genetics programs and to serve as a national resource center for information and education in the areas of newborn screening and genetics.

4.      **The MCH Neighborhood** http://mchneighborhood.ichp.edu/

Support and training for the development of web-sites for projects funded by the Maternal and Child Health Bureau. MCH Neighborhood will host your site free of charge and will provide you with exclusive password-protected remote access privileges so that you may keep your site up-to-date and dynamic -- from wherever you may be located.

5.      **Family Voices** http://www.familyvoices.org/

Families and friends speaking of behalf of children with special health care needs.

This resource list was prepared by HRSA with input from CDC and NIH for the "3rd National Conference on Genetics and Public Health: Connecting Research, Education, Practice & Community", September 19-20, 2000 in Ann Arbor, Michigan.  This list was last updated on August 17, 2000.

**Genetics in Primary Care**
**Additional Resources on the World Wide Web**

- **GROW (Genetics Resources on the Web) Search Tool**: http://search.info.nih.gov/grow/

  GROW is a search tool for genetics resources that is in the early stages of development. Using search terms, you are provided with a ranked listing of useful web resources for your query.  15,000 references are currently archived.

- **Image Archive on the American Eugenics Movement**: http://vector.cshl.org/eugenics/

  In this Archive, you can search the original materials from the Eugenics Record Office at Cold Spring Harbor.  The Cold Spring Harbor Laboratory was the center of American eugenics research from 1910-1940.  In the Archive you will see numerous reports, articles, charts, and pedigrees that were considered scientific "facts" in their day.

- **CDC Prevention Guidelines**:
  http://aepo-xdv-www.epo.cdc.gov/wonder/prevguid/prevguid.htm

  The Prevention Guidelines Database is a comprehensive compendium of all of the official guidelines and recommendations published by the US Centers for Disease Control and Prevention (CDC) for the prevention of diseases, injuries, and disabilities. This compendium was developed to allow public health practitioners and others to quickly access the full set of CDC's guidelines from a single point, regardless of where they were originally published.

### Genetics in Primary Care (GPC): A Faculty Development Initiative

The *Genetics in Primary Care (GPC): A Faculty Development Initiative* is a contract funded in 1998 by the Maternal and Child Health Bureau, and the Bureau of Health Professions of the Health Resources and Services Administration (HRSA) with co-funding from:

➢ National Human Genome Research Institute, National Institutes of Health
➢ Agency for Healthcare Research and Quality

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**GOAL OF GPC**
*To enhance the ability of faculty to incorporate the clinical application of genetic information into undergraduate and graduate primary care medical education*

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GPC's Scope of Work is to plan, implement, and evaluate outcomes of training programs in genetics. GPC training programs target family medicine, general internal medicine and general pediatrics faculty.

During the first phase (18 months) of the GPC, an interdisciplinary GPC Executive Committee and Advisory Committee representing 37 organizations (see attached list) engaged in considerable discussion concerning the design of the GPC Training Program. A ten-member Genetics Education Consultant Committee has brought genetics education expertise to the Project. An external evaluation team from the Medical College of Wisconsin is conducting an evaluation of the Program, using the CIPP model of examining context, input, process and product.

At the beginning of Phase II of the project, a competitive process was used to select twenty faculty teams from across the country to participate in the GPC Training Program. Objectives of the GPC Training Program are:

♦ To increase the number of primary care (family medicine, general internal medicine, and general pediatrics) physician faculty in the United States who are trained to conduct faculty development and training activities in genetics in a culturally competent manner with other primary care faculty responsible for the education of medical students and training of primary care residents;

♦ To train a mix of primary care faculty including faculty whose primary responsibilities are clinical teacher, teacher/researcher/administrator, or leader;

♦ To develop varying models for faculty development in genetics for primary care faculty which address various faculty whose roles are clinical teacher, teacher/researcher/administrator, or leader;

♦ To develop a primary care faculty development curriculum in genetics which: a) is adaptable to a variety of settings with primary care faculty responsible for educating medical students and/or training primary care residents; b) enables primary care faculty to teach content and concepts which are at the core of the contextual interface between genetics and primary care; and c) is attentive to issues of cultural and ethnic diversity.

Key elements of the GPC Training Program:

♦ Train-the-trainer program for twenty faculty teams
♦ Two training sessions for faculty teams, one held October 2000 and the second held April 2001
♦ Between and following the two training sessions, teams implement faculty development activities at home institutions or programs
♦ Executive, Advisory, Genetics Education Consultant Committee teams conducted site visits to faculty teams between two training sessions (visits conducted February – April 2001)
♦ Faculty teams have provided feedback critical to improving the GPC Training Program and the GPC Curriculum.

## Current Status

*GPC External Evaluation*
➢ GPC External Evaluation Team is continuing collection of data pertinent to outcomes of twenty teams' participation in the GPC Training Program

*GPC Curriculum*
➢ The GPC Curriculum has been revised according to input received through participants of the GPC Training Program
➢ The September 2001 revision of the GPC Curriculum will soon be available at: *Genes-r-us.uthscsa.edu*
➢ Future revisions to the GPC Curriculum are planned through a separate contract under the leadership of the Director of the GPC Training Program

## Continuation of Phase II of GPC Activity

Based on input received from the GPC Advisory Committee and GPC faculty team members, information from site visit reports, and from GPC External Evaluation Team reports, Phase II activity of the GPC has been extended for twelve months. The purpose of this continuation of Phase II is to develop collaborative products which will enhance faculty development activities at teams' home institutions and also be of potential national benefit.

These GPC Products to be developed will focus on
✓ Family history taking
✓ Red flags
✓ Cultural competency
✓ Evidence-base for genetics in primary care

Following completion of Phase II, recommendations to the Federal government will be made during Phase III by the GPC Executive Committee with input from the Advisory Committee.

## *GPC Advisory Committee Organizations and Liaisons*

# *ORGANIZATIONS*

PRIMARY CARE ORGANIZATIONS

*Family Medicine*
Society of Teachers of Family Medicine
American Academy of Family Physicians
Society of Teachers of Family Medicine Group on Predoctoral Education
Association of Departments of Family Medicine
Association of Family Practice Residency Directors
American Board of Family Practice

*Internal Medicine*
Society of General Internal Medicine
American College of Physicians-American Society of Internal Medicine
Clerkship Directors in Internal Medicine
Association of Professors of Medicine
Association of Program Directors in Internal Medicine
American Board of Internal Medicine

*Pediatrics*
Ambulatory Pediatric Association
American Academy of Pediatrics
Council on Medical Student Education in Pediatrics
Association of Medical School Pediatric Department Chairmen
Association of Pediatric Program Directors
American Board of Pediatrics

*Osteopathy*
American Osteopathic Association
American Association of Colleges of Osteopathic Medicine
American College of Osteopathic Family Physicians

*Other*
Medicine-Pediatric Program Directors Association


GENETICS ORGANIZATIONS

American College of Medical Genetics
American Society of Human Genetics
Alliance of Genetic Support Groups
Association of Professors of Human Genetics

SPECIALTY ORGANIZATIONS

American College of Obstetricians and Gynecologists
Association of Professors of Gynecology and Obstetrics
Association of Teachers of Preventive Medicine


OTHER ORGANIZATIONS
American Medical Association
American Medical Student Association
National Medical Association
National Hispanic Medical Association
Asian and Pacific Islander American Health Forum
Association of American Medical Colleges
Association of Schools of Public Health
American Association of Health Plans


## LIAISONS

National Human Genome Research Institute, National Institutes of Health
Agency for Healthcare Research and Quality
Centers for Disease Control and Prevention

**Genetics in Primary Care (GPC): A Faculty Development Initiative**
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