Learning Objectives

After viewing this presentation, one should be able to:

• List three benefits of taking family history in medical practice
• Create a pedigree using standard symbols
• Identify five genetic red flags
• Know how to locate family history tools
• Know how to locate a genetics professional
• Use the core competencies to interpret family histories in case examples
Why Family History?

• **Single-gene disorders:**
  Knowledge of family history can aid in the diagnosis and treatment of rare single-gene disorders such as cystic fibrosis, fragile X syndrome, Huntington disease, or familial hypercholesterolemia.

• **Common, complex diseases:**
  Family history has been shown to be a major risk factor for many chronic diseases such as cardiovascular disease, cancer, mental illness, and asthma.
  ⇒ Family history may be the primary risk factor!
Why Family History?

Inform diagnosis

Change management

Promote risk assessment and stratification

Build rapport with patients
Prioritizing Information

Comprehensive vs. targeted family history

**Comprehensive**
- General healthcare setting
- Elicit general health information about relatives
  1) Major medical concerns
  2) Chronic medical conditions
  3) Hospitalizations, surgeries
  4) Birth defects
  5) Mental retardation, learning disabilities, developmental delay

**Targeted**
- Specialized clinical setting or evaluation for specific concerns
- Specific information about the condition of concern
1) Recognize, understand, and use standard pedigree symbols

2) Produce at least a three-generation pedigree that includes:

- Identification of the patient

Identify the patient, or **consultand**, with an arrow
• Identification of the **proband**: The **proband** is the affected individual who brings the family to medical attention

(A **consultand** is often also a **proband**)
Collection

• When the **proband** is not the **consultand**:

In this case, the patient’s sister is the first person to bring the family to medical attention.
2) Produce at least a three-generation pedigree that includes:

- Patient’s first-, second-, and third-degree relatives
- Information on maternal and paternal relatives
- Representation of “full” from “half” relationships
  example: children with same or different partner
- Affected and unaffected relatives
2) Produce at least a three-generation pedigree that includes:

- Identification of the historian, or person providing the information
  - May be the patient or someone else, such as a parent
- Date of collection (or date of update), and name of collector (or updater)
- Legend or key, if symbols are used to designate disease
Collection

Degrees of Relationship

First-degree relatives: parents, siblings, children

Second-degree relatives: half-siblings, aunts, uncles, grandparents, nieces & nephews

Third-degree relatives: first cousins
Collection

Maternal and paternal relatives
3) Elicit the following information for individuals represented in pedigree as required for clinical indications:

- Age, birth date, or year of birth
- Relevant health information
- Diagnosis, age at diagnosis
- Age at death, or years of birth/death
- Cause of death
- Ethnic background for each biological grandparent

3) Elicit the following information for individuals represented in pedigree as required for clinical indications:

- Infertility, or no children by choice
- Consanguinity
- Pregnancies
- Pregnancy complications (note gestational age)
  - Miscarriages
  - Stillbirths
  - Ectopic pregnancies
  - Pregnancy terminations
  - Preterm birth
  - Preeclampsia
  - Bleeding/clotting complications

Collection

- Identification of patient
- Patient’s first-, second-, and third-degree relatives
- Information on maternal and paternal relatives
Collection

- Degree of relationship
  - Distinguish “full” from “half” relationships
- Age, birth date, or year of birth
- Relevant health information
- Age at, or year of death
- Cause of death

- d. 70’s “natural causes”
- d. mid 60’s dementia
- d. 54 yo accident
  - 40 yo
  - 38 yo
- 61 yo
- 55 yo depression
- 60 yo lung cancer
- 59 yo high cholesterol
- d. 55 yo heart attack
- d. late 60’s cancer (colon?)
- 63 yo

- 35 yo
  - 2 yo
  - 5 mo
  - “hole in heart”
- 32 yo
- 30 yo
- 6 yo
- 1.5 yo
Collection

- Diagnosis, age at diagnosis
- Affected and unaffected individuals

[Genetic tree diagram showing family members with various causes of death including dementia, heart attack, depression, lung cancer, and high cholesterol, with specific ages and other family details]
Collection

- Pregnancies
- Pregnancy complications (note gestational age)
- Infertility, or no children by choice
Collection

- Ancestral background for each biological grandparent
- Consanguinity

*no consanguinity reported*

N. European

- d. 70s
  - 61 yo
  - d. 54 yo accident

- d. mid 70s
dementia, mid 60s

- 55 yo depression, 42 yo
  - by choice

German, English, American Indian

- d. 55 yo
  - heart attack
  - d. late 60s
    - ca. (colon?), late 60s

- 59 yo high cholesterol

- by choice

- 63 yo

Additional details:

- 40 yo
- 38 yo
- 35 yo
- 60 yo
- 32 yo
- 30 yo

- “hole in heart”
- “natural causes”
- accident
- lung ca.
- by choice
- high cholesterol

- 2 yo
- 5 mo
- 3 yo
- 1.5 yo
Collection

- Legend or key, if symbols are used to designate disease
- Date of collection (or update), name of collector (or updater)

*no consanguinity reported*

Key:
- dementia
- cancer
- depression
- born with “hole in heart”

N. European

- d. 70s
  - “natural causes”
  - d. 54 yo accident
  - 61 yo
  - d. mid 70s
  - dementia, mid 60s
  - 55 yo depression, 42 yo
  - by choice
  - 35 yo

German, English, American Indian

- d. 55 yo heart attack
  - 60 yo
  - lung ca., 58 yo
  - high cholesterol
  - 59 yo
  - 32 yo
  - 30 yo

Collected by: Jane Doe
Collected on: August 20, 2006
Additional Standard Pedigree Symbols

“2 males”
“4 females”

“Unknown number or multiple children, males and females”

No children-infertility

“3 females”

Consanguinity: Relationships

First cousins

First cousins once removed

Second cousins

Consanguinity: An Example

Additional Standard Pedigree Symbols

Affected Individuals

Presymptomatic Individual

Fraternal Twins (dizygotic)

Identical Twins (monozygotic)

Additional Standard Pedigree Symbols

Additional Standard Pedigree Symbols

- Sperm donor
- Egg donor
- Egg donor/gestational carrier

2) Recognize Genetic Red Flags:

Do you think a condition present in a family may be genetic? Look for these clues:

- Family history of known or suspected genetic condition
- Multiple affected family members with same or related disorders
- Earlier age at onset of disease than expected
- Developmental delays or mental retardation
Interpretation

2) Recognize Genetic Red Flags (cont.):

Do you think a condition present in a family may be genetic? Look for these clues:

- Diagnosis in less-often-affected sex
- Multifocal or bilateral occurrence in paired organs
- One or more major malformations
- Disease in the absence of risk factors or after preventive measures
Interpretation

2) Recognize Genetic Red Flags (cont.):

Do you think a condition present in a family may be genetic? Look for these clues:

- Abnormalities in growth (growth retardation, asymmetric growth, excessive growth)
- Recurrent pregnancy losses (2+)
- Consanguinity (blood relationship of parents)
- Ethnic predisposition to certain genetic disorders
Pedigrees

- Pedigree: uses standard symbols and terminology to represent a large amount of information in a diagram
- Preferred method of organizing and displaying family history
- Benefits:
  1) organize a great deal of information
  2) visualize inheritance patterns and familial clustering
Interpretation

1) Recognize basic inheritance patterns:

**Multifactorial disorders**
- Multiple genetic and environmental factors

**Single-gene disorders**
- Autosomal Dominant
- Autosomal Recessive
- X-Linked

**Chromosomal disorders**
- Extra/missing chromosomes
- Large-scale deletions or duplications
- Translocations

**Mitochondrial disorders**
- Characterized by maternal transmission
- Usually neurological or neuromuscular symptoms
Multifactorial Inheritance

Familial Clustering

- alcoholism
- d. suicide
- anxiety/depression
- ADHD
- depression
- mood disorder
Single-gene Inheritance
Autosomal Dominant
Single-gene Inheritance
Autosomal Recessive

[Genetic diagram showing the inheritance pattern of autosomal recessive traits]
Single-gene Inheritance

X-Linked
Mitochondrial Inheritance
Chromosomal Translocation

CHD= Congenital heart defect
CP= Cleft palate
MR= Mental retardation
SAB= Spontaneous abortion
SS= Short stature

= balanced translocation carrier
Interpretation

Pedigrees or Checklists?

Crucial element: THE INFORMATION!

The method used must:

1) be reasonably accurate
2) be updated easily
3) allow for pattern detection and interpretation
4) provide clear communication and interpretation between healthcare providers

Opportunities for Patient Education

Eliciting and summarizing family history information can:

- help the patient understand the condition in question
- clarify patient misconceptions
- help the patient recognize the inheritance pattern of the disorder
- demonstrate variation in disease expression (such as different ages at onset)
- provide a visual reminder of who in the family is at risk for the condition
- emphasize the need to obtain medical documentation on affected family members

Interpretation

Complicating Factors in Interpretation

1) Missing information vs. unaffected relatives
2) Reliability of information
3) Non-traditional families
4) Unknown paternity
5) Adoption
6) Cultural definitions of family
7) Cultural biases
8) Consanguinity
9) Confidentiality
Intervention

1) Identify where more specific information is needed and obtain records

2) Assess general risks

3) Know when to refer to genetics professionals

4) Encourage the patient to talk to other family members

5) Update pedigree at subsequent visits
Risk Classification

- Family History Tool
  - Average
    - Standard public health prevention recommendations
  - Moderate
    - Personalized prevention recommendations
  - High
    - Personalized prevention recommendations and referral for genetic evaluation
Available Family History Tools

Surgeon General’s Family History Initiative: 
“My Family Health Portrait”

www.hhs.gov/familyhistory, familyhistory.hhs.gov
Available Family History Tools

“Family History: Resources and Tools” (CDC)

www.cdc.gov/genomics/public/famhistMain.htm
Available Family History Tools

AMA’s Genetics & Molecular Medicine: Family History

www.ama-assn.org/ama/pub/category/2380.html

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Family History

* e-mail story | print story

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The importance of a family history
Describes importance of family medical history in disease prevention and provides links to resources on how to collect family history information and generate a simple pedigree.

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Prenatal screening questionnaire

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Pediatric clinical genetics questionnaire

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Adult family history form

Last updated: Jun 20, 2006
Content provided by: AMA Science
Available Family History Tools

“Your Family History- Your Future”
(NSGC, Genetic Alliance, ASHG)

YOUR FAMILY HISTORY – YOUR FUTURE

Your family history holds key information about your past and clues to your future health. Many of your physical traits (such as eye color, hair color, and height) are inherited. So, too, are risks for certain genetic conditions and health problems such as heart disease, diabetes, and some cancers. You may have noticed that some of your relatives are healthier and live longer than other relatives. You may also have noticed that some relatives have the same health problems. By collecting your family’s health history, you can learn what health problems you may be at increased risk for in the future and how to reduce your risks. For instance, people at increased risk for heart disease may be able to reduce their risk through not smoking, regular exercise and diet. Finding out your family history can benefit both you and your relatives… and it can be fun too!
How to Find a Genetics Professional

1. National Society of Genetic Counselors

Find a counselor according to location, institution, or area of specialization

www.nsgc.org
How to Find a Genetics Professional

2. GeneClinics

Welcome to the GeneTests Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the terms of use.

At This Site
- GeneReviews
  Online publication of expert-authored disease reviews
- Laboratory Directory
  International directory of genetic testing laboratories
- **Clinic Directory**
  International directory of genetics and prenatal diagnosis clinics
- Educational Materials
  - Illustrated glossary
  - About genetic services
  - PowerPoint® slide presentations

A voluntary listing of US and international genetics clinics providing genetic evaluation and genetic counseling

www.geneclinics.org
How to Find a Genetics Professional

3. American Society of Human Genetics

www.ashg.org
Case Examples
A new patient, Saundra, states that many individuals in her family have had cancer, especially colon cancer. She is certain that she is destined to develop cancer in the near future.
Saundra’s Family

How can taking Saundra’s family history help to assess her risk to develop colon cancer?

1) Identify specific relatives with colon or other cancers
2) Identify the ages at the diagnosis of cancer
3) Identify family members who have not had cancer
4) Identify the side (or sides) of the family on which cancer is present
Do you think that Saundra has a low, moderate, or high risk of developing colon cancer based on her family history?

How did you assess her risk?
Saundra’s Family

Do you think that Saundra has a low, moderate, or high risk of developing colon cancer based on her family history?

How did you assess her risk?
Saundra’s Family

Factors decreasing risk of genetic basis to condition in first scenario

- Cancers common in general population
- Affected relatives are older at diagnosis
- Cancer on both sides of family

Factors increasing risk of genetic basis to condition in second scenario

- Affected relatives are relatively young at diagnosis
- Multiple affected relatives concentrated on same side of family
Saundra’s Family

Utility of family history tools:

• **Collection**
  Focus on diagnoses and ages, as well as affected and unaffected individuals

• **Interpretation**
  Consider red flags: multiple affected family members, early age at onset

• **Implementation**
  Assessment of risk alters recommended surveillance
During a routine visit, Toby mentions that he is extremely conscious of his physical health because he does not want to get heart disease like the other members of his family.
Toby’s Family

How can taking Toby’s family history help to assess his risk to develop heart disease?

1) Identify specific relatives with heart disease and associated complications
2) Identify the ages at onset of disease
3) Identify the presence or absence of risk factors in relatives with heart disease
Do you think that Toby has a low, moderate, or high risk of developing heart disease based on his family history?

How did you assess his risk?
Toby’s Family

Do you think that Toby has a low, moderate, or high risk of developing heart disease based on his family history?

How did you assess his risk?
Factors decreasing risk of genetic basis to condition in first scenario

- Affected family members have multiple risk factors, some of which are environmental
- Affected relatives are older at diagnosis

Factors increasing risk of genetic basis to condition in second scenario

- Affected relatives are relatively young at diagnosis
- Disease in the absence of risk factors
Utility of family history tools:

- **Collection**
  
  Focus on diagnoses and ages at onset; also consider presence or absence of risk factors

- **Interpretation**
  
  Consider red flags: multiple affected family members, early age at onset, disease in the absence of risk factors and in the less-often-affected sex

- **Implementation**
  
  Assessment of risk alters recommended testing and health management
Maria (one month old) was born with a cleft lip and palate (CL/P). CL/P is commonly isolated, but can also be a part of a number of different inherited syndromes.
Baby Maria’s Family

How can taking Maria’s family history help assess whether her CL/P is isolated or syndromic?

1) Identify whether features are present in other family members that are suggestive of a syndrome

2) If features are present, identify an inheritance pattern

Why is this helpful?

- Better management of associated health problems
- Determine recurrence risk for future children
Baby Maria’s Family

Key:

- Cleft lip and palate

Do you think that there is a low, moderate, or high chance that Maria’s cleft lip and palate is due to an inherited condition?

How did you assess this chance?
Isolated Cleft Lip and/or Palate:

- 1 in 1000 births (0.1%)
- Recurrence risks
  - Maria’s sibling: 2%-8%
  - Maria’s child: 4%-6%
Do you think that there is a low, moderate, or high chance that Maria’s cleft lip and palate is due to an inherited condition?

How did you assess this chance?
Baby Maria’s Family

22q Deletion syndrome:
- Deletion of submicroscopic deletion of ch. 22q
- Inheritance: autosomal dominant
- Recurrence risks:
  - Maria’s sibling: 50%
  - Maria’s child: 50%
- Primary features:
  - Congenital heart defects
  - Immune deficiency
  - Cleft lip and palate
  - Hypocalcemia
  - Learning difficulties
  - Characteristic facies
Factors decreasing risk of inherited syndrome in first scenario

- Presence of non-specific health conditions common in the general population
- Features on both maternal and paternal sides
- No clear inheritance pattern or family clustering

Factors increasing risk of inherited syndrome in second scenario

- Clustering of potentially related features
- Several genetic red flags are present
- Clear autosomal dominant inheritance
Utility of family history tools:

- **Collection**
  Specifically ask about features that are often seen in syndromes associated with CL/P

- **Interpretation**
  Consider red flags: multiple affected family members, early age at onset, developmental delays, one or more major malformation

- **Implementation**
  Presence of a syndrome can alter recurrence risks and health management for the patient and family members
Anne and Geoff want to start a family. Following ACOG guidelines, Anne’s physician makes cystic fibrosis (CF) carrier screening available to all her patients, and recommends screening to her patients who are Northern European (including Ashkenazi Jewish) or who have a family history of CF.
Anne and Geoff

How can Anne and Geoff’s family histories help the physician decide whether to recommend CF carrier testing or simply make it available to Anne and Geoff?

1) Identify whether CF is present in the family
2) Determine whether Anne or Geoff are of ancestries for which CF carrier screening is recommended
3) Identify other family members who may consider carrier testing
Anne and Geoff

Cystic Fibrosis:

• Multisystem disease
  – Pulmonary: accumulation of mucus
  – Digestive: malnutrition and constipation
  – Reproductive: bilateral absence of vas deferens (infertility)

• Inheritance: autosomal recessive

• Average life span: young adulthood
Anne and Geoff

Northern European, Russian

- 56 yo high BP (early 40s)
  - 34 yo irritable bowel syn. (31 yo)
  - 7 yo
  - 4 yo
  - 3 yo

African American, American Indian

- 59 yo diabetes (mid 40’s)
  - 57 yo blood clot- leg (54 yo)
  - 56 yo
  - 57 yo
  - 59 yo

Do you think that there is a low, moderate, or high chance that either Geoff or Anne are carriers of a CF mutation?

How did you assess this chance?
Anne and Geoff

Northern European, Russian

56 yo

34 yo

irritable bowel syn. (31 yo)

7 yo

57 yo high BP (early 40s)

4 yo

30 yo

28 yo migraines (late teens)

3 yo

Northern European

59 yo diabetes (mid 40's)

25 yo

mitral valve prolapse (mid 20's)

2 yo

57 yo blood clot - leg (54 yo)

2 yo born at 37 wks

Do you think that there is a low, moderate, or high chance that either Geoff or Anne are carriers of a CF mutation?

How did you assess this chance?
Anne and Geoff

Factors **decreasing** risk of being a CF carrier in first scenario

- Anne’s ancestry has a lower carrier frequency
- No family history

Factors **increasing** risk of being a CF carrier in second scenario

- Both Anne and Geoff are of Northern European ancestry
- Positive family history: Anne’s nephew (second-degree relative) has CF
Utility of family history tools:

• **Collection**
  Elicit ancestry of biological grandparents, relevant health information

• **Interpretation**
  Consider red flags: known family history, ethnic predisposition; autosomal recessive inheritance

• **Implementation**
  Assessment of risk determines whether carrier testing is offered; may also consider prenatal testing, pregnancy surveillance, or preparation for CF management
Acknowledgments

Funded by Audrey Heimler Special Projects Grant of the National Society of Genetic Counselors

Created as part of a thesis project for completion of the Master’s Program in Genetic Counseling, University of Maryland, Baltimore

Contributors:

- Emily Malouf, MGC
- Robin Bennett, MS, CGC
- Siobhan Dolan, MD, MPH
- Erin Harvey, ScM, CGC
- Joseph McInerney, MA, MS
- Paula Yoon, ScD, MPH
- Members of NCHPEG’s Family History Working Group