Objectives

• Understand the role of the general internist in genetic testing

• Recognize patients at high risk for genetic disorders

• Review ethical, legal and psychological impacts of genetic testing
Role of the General Internist

- Obtaining family history
- Assessing risk information
- Identifying patients appropriate for consultation
- Coordinating long term management
Family History

• Initial step in assessing inherited risks

• No clear cut best method

• Useful in stratifying risk

• Not routinely done
Family History: Collection

• Up to second degree relatives
  – Grandparents
  – Grandchildren
  – Aunts, uncles and first cousins

• Only “blood” relatives
Family History: SCREEN

• **Some Concerns**: Do you have (some) concerns about diseases or conditions that seem to run in your family?

• **Reproduction**: Have there been any problems with pregnancy, infertility or birth defects in your family?
Family History: SCREEN

- **Early disease, death or disability:** Have any members of your family been diagnosed with a chronic disease at an early age or have members of your family died at an early age?
Family History: SCREEN

- **Ethnicity:** How would you describe your ethnicity? What country did your ancestors come from?

- **Non-genetic conditions:** Are you aware of any non-medical conditions or risk factors, like smoking or problem drinking in your family?
Family History: Collection

• Family size

• Consanguinity

• Siblings – often forgotten

• Encourage patients to complete history
Family History: Collection

- Condition(s) reported
- Relationship of affected individual to the patient
- Age of relative at onset of condition
https://familyhistory.hhs.gov/fhh-web/home.action
Pedigree of autosomal dominant inheritance

Multiple generations are affected.

Courtesy of Linda Pinsky, MD.
# AAFP GENES Red Flags

<table>
<thead>
<tr>
<th>Features</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group of congenital anomalies</strong></td>
<td>While anatomic variation is normal, the presence of multiple variations may be indicative of a genetic syndrome.</td>
</tr>
<tr>
<td><strong>Extreme or exceptional presentation of common conditions</strong></td>
<td>Examples of this include the onset of disease at a younger than average age, unusually severe presentation of illness, multiple primary cancers, recurrent miscarriages.</td>
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<tr>
<td><strong>Neurodevelopmental delay or degeneration</strong></td>
<td>Developmental delay or regression in children and early onset dementia in adults may be a sign of a genetic condition.</td>
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<tr>
<td><strong>Extreme or exceptional pathology</strong></td>
<td>Some tumor pathologies may be suggestive of an inherited condition. Examples include medullary thyroid cancer, pheochromocytoma, plexiform neurofibromas, and multiple colon polyps.</td>
</tr>
<tr>
<td><strong>Surprising laboratory values</strong></td>
<td>Certain laboratory values may indicate an inherited defect in metabolic or clotting pathways. Examples include elevated fasting transferrin-iron saturation and cholesterol level &gt;500 mg/dL.</td>
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</tbody>
</table>
Key Red Flags

• History of consanguinity (diseases caused by rare recessive mutations are more common in families with matings of related individuals).

• Consanguinity is generally more relevant to defining risk in the pediatric evaluation, than for conditions with adult onset.
Patterns: Autosomal Dominant

- Multiple generations
- Male and female
Patterns: Autosomal Recessive

- Siblings more likely than parents
- Male and female
Patterns: X-linked Recessive

- Males
- Related through mothers
Limitations to History

• Small family size or gender underrepresentation
• Uncertainty in percentages
• Disease prevention
• De novo mutations and incomplete penetrance
### Interpreting the History

<table>
<thead>
<tr>
<th>Average Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No known family history, <strong>OR</strong></td>
<td>• One first degree relative (FDR) with onset of disease at an average age, <strong>OR</strong></td>
<td>• Premature disease or unusual presentation in an FDR</td>
</tr>
<tr>
<td>• Only one second or more distantly related relative</td>
<td>• Two second degree relatives (SDR) on the same side of the family*</td>
<td>• 2 ≥ affected FDRs*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2 ≥ SDRs, with at least one having premature onset*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 3 ≥ affected relatives*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moderate risk status on both sides of the family</td>
</tr>
</tbody>
</table>

* Relatives must be on the same side of the family.
Benefits of Genetic Counseling

• Individuals often have mistaken understanding of their risk

• Research or registry opportunities may exist

• Some families may choose to bank DNA
Indications: Moderate Risk

• Two to three-fold risk increase

• Usually due to:
  – Environment
  – Lifestyle
  – Low penetrance genetics

• No indications for genetic evaluation
Indications: High Risk

- Fifty percent or greater lifetime risk

- Earlier age of onset of disease
  - Colorectal cancer
  - Breast cancer

- Candidates for full genetic evaluation
Barriers Genetic Counseling

• Possible only 17% of potential patients are referred because:
  – Perceived lack of benefit
  – Uncertainty of incorporating genetic information
  – Lack of clinician awareness
  – Lack of awareness or availability of genetic tests or counselors
  – Patient reluctance
  – Fear that something harmful will be found
  – Cost and reimbursement issues
Information to Send to Counselor

• Specific questions to be addressed

• A summary of available family history

• A summary of the patient's pertinent medical history, including laboratory test results or biopsy reports, where relevant.
Content of Counseling

• Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
• Education about inheritance, testing, management, prevention, resources and research.
• Counseling to promote informed choices and adaptation to the risk or condition.
Content of Counseling: Risk Assessment

• What genetic testing is available and what test results may mean for the patient

• How to modify that risk, if possible

• How to deal with the information as it pertains to medical management, emotional response, and family dynamics
<table>
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<tr>
<th>Purpose</th>
<th>Examples</th>
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<tr>
<td>Pre-implantation testing</td>
<td>Pre-implantation testing, for high risk couples, is performed on embryos resulting from in vitro fertilization.</td>
</tr>
<tr>
<td>Prenatal testing</td>
<td>Prenatal testing identifies conditions in which a mutation has been identified in a parent.</td>
</tr>
<tr>
<td>Diagnostic testing</td>
<td>Diagnostic genetic testing is used to support a specific diagnosis in a patient with an existing condition. (1800)</td>
</tr>
<tr>
<td>Predictive testing</td>
<td>Predictive testing is a method of risk assessment for unaffected individuals who are at risk for developing conditions with a hereditable component.</td>
</tr>
<tr>
<td>Carrier testing</td>
<td>Carrier testing is used to identify asymptomatic individuals who are heterozygous for a mutation that causes a genetic disorder in homozygotes.</td>
</tr>
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</table>
Predictive values

• Penetrance - likelihood of developing disease given inheritance of a disease-causing mutation

• Variable expressivity - phenotypic variations in the way the disease is expressed
Validity and Utility

• Validity - the ability of a genetic test to predict a disease phenotype

• Examples:
  – APC gene - virtually all individuals who test positive will develop familial adenomatous polyposis (FAP)
  – APOE e4/e4 genotype - 30 percent chance of developing Alzheimer's disease
Ethical, Legal, & Psychosocial Issues

• Psychosocial issues require not just an understanding of the patient, but of the dynamics of the patient's family.

• Concern about the potential for loss of health insurance or employment opportunities. This is particularly true for the unaffected individual and their unaffected extended family members.
Genetic Information Nondiscrimination Act (GINA)

- Enacted in 2008
- Prohibits discrimination by health insurers and employers on the basis of genetic information.
- Most states also have additional legislation protecting against the use of genetic information by health insurers and employers.
Ethical, Legal, & Psychosocial Issues

• Potential ethical or legal obligation of a physician to disclose genetic information to other at-risk family members.
  – Duty to protect patient privacy and autonomy
  – Duty to disclose for the purpose of preventing future harm
Ethical, Legal, & Psychosocial Issues

- Genetic testing for conditions that most commonly manifest in adults is generally not done in children and adolescents unless a preventive intervention is effective only if done during those time periods.
Informed Consent

• Patient is able to voluntarily exercise free power of choice, without any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion. (Department of Health, Ed. & W)

• Exceptions:
  – Newborn screening (opt-out)
  – Pediatrics
Follow-up

- More aggressive screening initiated at an earlier age
- Counseling for lifestyle modifications
- Initiation of pharmacologic or surgical interventions
- Management of related psychosocial issues
Review

- Testing can be diagnostic or predictive
- Primary care physicians are front line
- Family history is the first step
- High risk patients should be referred for genetic counseling
Review

• Ethical, legal and psychosocial ramifications are significant

• Consider the individual and the family

• Offer long term support
QUESTIONS?

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References

• Raby, BA, Kohlmann, W, Venne, V. Genetic counseling and testing. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2012.

## Resources for collecting family history information

<table>
<thead>
<tr>
<th>Resource</th>
<th>URL</th>
<th>Content</th>
</tr>
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<tr>
<td>Ohio State University Comprehensive Cancer Center - James Cancer Hospital</td>
<td><a href="http://www.jamesline.com/patientsandvisitors/prevention/">http://www.jamesline.com/patientsandvisitors/prevention/</a></td>
<td>Online resource which provides cancer risk assessment based on family history.</td>
</tr>
</tbody>
</table>