Genetics into Family Practice Workshop

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Case Studies in Personalized Medicine

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Disclosures

- **Disclosure of Relevant Financial Relationships:** The presenter has no financial relationships to disclose.
- **Disclosure of Off-Label and /or Investigative Uses:** The presenter will not discuss off label use and /or investigational use in this presentation.

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Objectives

- Analyze case studies involving genomic medicine.
- Appraise the validity of the genomic information in each case.
- Discuss the relevant bioethical issues in each case.
- Draft an educational format for genomics in primary care

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ACCE Framework

- **Analytical validity** – genomic test results need to be accurate and reliable.
- **Clinical validity** – reliable results are of consistent clinical significance.
- **Clinical utility** – there is a clear benefit for intervention based on genomic test results.
- **Ethical, legal**, and **social** implications are openly discussed.

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Tiered Approach to Integrating Genomics into Practice

- Tier 1 – recommended for clinical use by evidence-based panels and supported by systematic review of evidence
- Tier 2 – validity and promising evidence of clinical utility, but lack evidence-based recommendations
- Tier 3 – inadequate validity or utility

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Caveat

- Genomic makeup in complex disease is ***probabilistic***, not ***deterministic***.

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Case No. 1

- Andrea is a 34-year-old bank executive.
- Her mother was diagnosed with breast cancer six years ago and is now disease free.
- Her father has Type II Diabetes.
- Her maternal grandfather is in a nursing home dementia unit.
- She jogs for exercise 5 days a week. She has about 5 drinks a week, usually wine. She occasionally smokes when drinking.
- Her BMI is 23 and she has no know medical problems.
  - *Adapted from Nuffield Council on Bioethics*

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Case No. 1

- Recently, she received an email offering her personal genetic testing to screen for genes that may put her at risk for future disease. The price was affordable and the process seemed simple. Curious to know her risk, she requests a kit and sends in a saliva sample.
- She makes an appointment to discuss her results with you.

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Andrea's Results

Condition	Est. Lifetime Risk	Avg. Population Risk
Alzheimer's Disease	19%	11%
Breast Cancer	13%	13%
Type II Diabetes	16.5%	19%
Heart Attack	38%	28%
Hypertension	40%	40%
Lung Cancer	4%	7.5%
Osteoarthritis	34%	33%

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Questions To Consider

- Does this testing benefit Andrea?
- She is concerned she is at increased risk for Alzheimer's Disease and Heart Attack. How would you discuss her increased risks?
- Are there modifiable environmental risks that might interact with genetic risks?
- Her husband's family has a history of premature MI (i.e. men younger than 55), and he takes cholesterol medication. She wants to know if she should have genetic testing for her 6-year-old son. What is your advice?

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Case No. 2

- James is a 42-year-old man coming in for his insurance-approved wellness exam.
- He has a history of hypertension. He smokes a pack of cigarettes a day, does not exercise and has 1-2 drinks a day. He describes himself as a "meat and potatoes" man and only occasionally eats fruits and vegetables.
- He has had no previous cancer screenings.
- His BMI is 28.
  - *Adapted from the National Coalition for Health Professional Education in Genetics*

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Case No. 2

- In his family history, James' older brother was diagnosed with colorectal cancer two years ago, at the age of 45. His mother was diagnosed with endometrial cancer at age 49. A paternal aunt was diagnosed with breast cancer at age 63. His maternal grandmother was diagnosed with pancreatic cancer at age 67.

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Questions to Consider

- Is James at average, increased (moderate) or high risk for colorectal cancer (CRC)?
- How should James be screened for CRC?
- Would you recommended for genetic counseling/testing for James?
- What would you recommend for James' 46-year-old sister?

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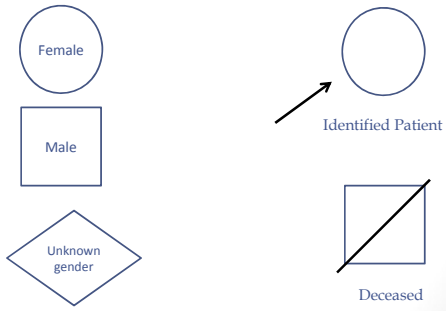
Creating a Pedigree



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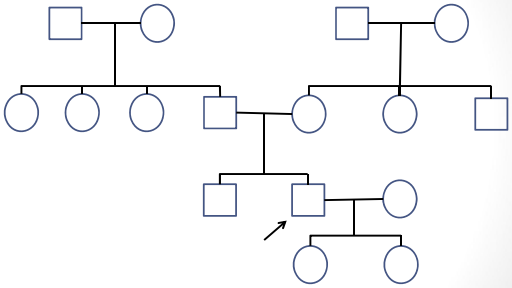

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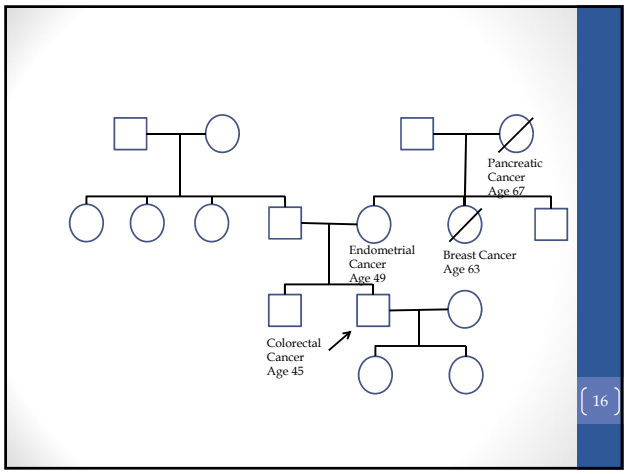
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Cancer
Age 67
Endometrial
Cancer
Age 49
Breast Cancer
Age 63
Colorectal
Cancer
Age 45
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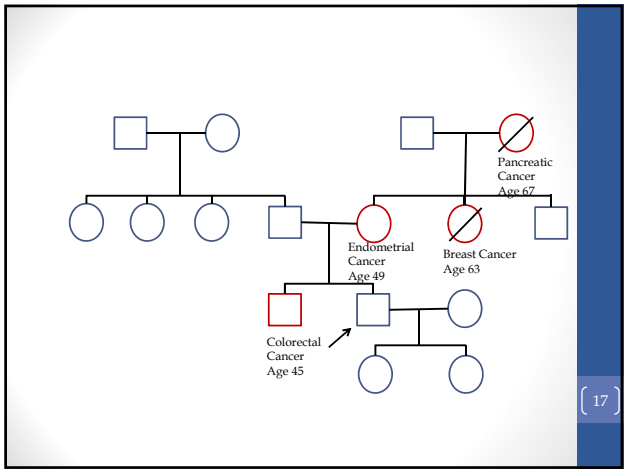
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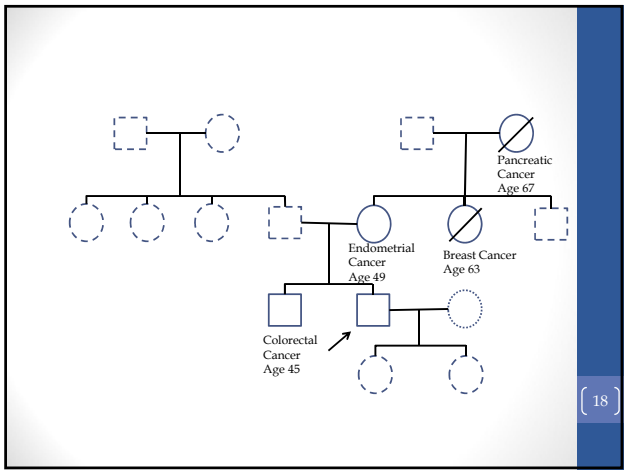
Pancreatic
Cancer
Age 67
Endometrial
Cancer
Age 49
Breast Cancer
Age 63
Colorectal
Cancer
Age 45
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Case No. 3

- Jasmine is a 22-year-old woman went to Planned Parenthood to start oral contraceptives.
- On her intake sheet at Planned Parenthood, she checked the box for a family history of blood clotting.
- She was told she had to have her doctor's permission before starting because of that history.

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Case No. 3

- Jasmine is a smoker, about 10 cigarettes a day.
- Her older sister has a six-month-old boy. The pregnancy was complicated by preecclampysia
- On her mother's side of the family, her uncle had a blood clot in his 30s and another in his 40s, and is now on blood thinners
- Her grandmother had a stroke at age 59.

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Questions to Consider

- If Jasmine stops smoking, has she eliminated her risk for developing venous thromboembolism on OCPs?
- Should anyone in Jasmine's family be tested for inherited thrombophilias?
- Should Jasmine be on anticoagulants?
- What forms of birth control would you recommend for Jasmine?

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Developing Genomic Education and Integration for Primary Care

- What key elements need to go into primary care education to manage genomics?
- Consider attitudes, knowledge, and skills.

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Attitudes

- All health professionals should:
  - appreciate the sensitivity of genetic information and the need for privacy and confidentiality.
  - seek coordination and collaboration with an interdisciplinary team of health professionals.
    - Core Competencies for All Health Care Professionals. National Coalition for Health Professional Education in Genetics. 2007. www.nchpeg.org

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Knowledge

- How identification of disease-associated genetic variations facilitates development of prevention, diagnosis, and treatment options.
- The interaction of genetic, environmental, and behavioral factors in predisposition to disease, onset of disease, response to treatment, and maintenance of health.
- The difference between clinical diagnosis of disease and identification of genetic predisposition to disease (genetic variation is not strictly correlated with disease manifestation).
  - Core Competencies for All Health Care Professionals.

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Knowledge

- The potential physical and/or psychosocial benefits, limitations, and risks of genetic information for individuals, family members, and communities.
- The ethical, legal and social issues related to genetic testing and recording of genetic information (e.g., privacy, the potential for genetic discrimination in health insurance and employment).
    - Core Competencies for All Health Care Professionals.

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Skills

- Explain effectively the reasons for and benefits of genetic services.
- Assure that the informed-consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question.
    - Core Competencies for All Health Care Professionals.

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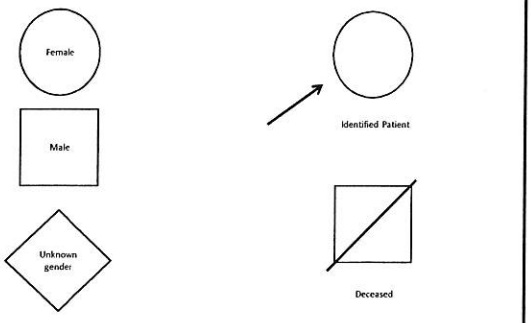
Creating a Pedigree



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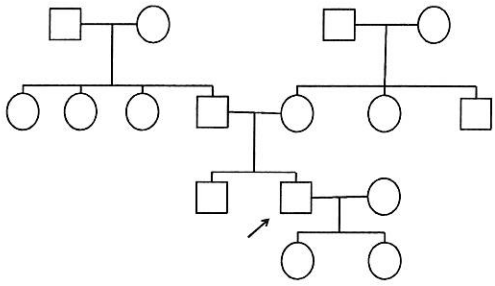

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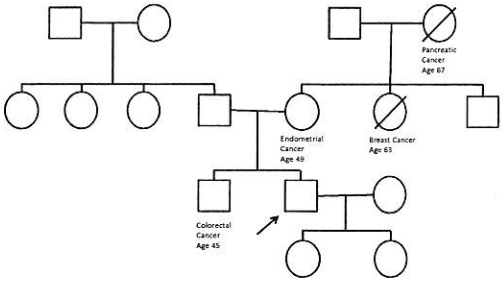

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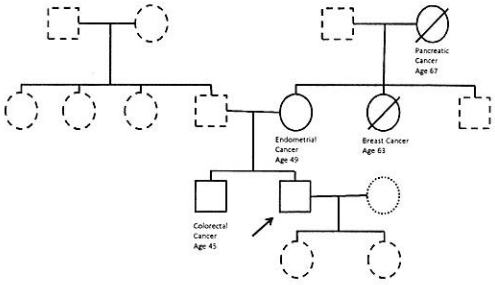

Lynch syndrome/hereditary non-polyposis colon cancer fact sheet

Clinical features
Lynch syndrome (LS) is caused by a mutation in a mismatch repair (MMR) gene. Individuals with LS are at increased risk for colon and other cancers, including gastric, urinary tract, brain, small bowel, pancreatic, hepatobiliary and sebaceous carcinoma. Women with LS are at increased risk for endometrial and ovarian cancer.

Diagnosis of LS
An individual should meet Amsterdam II criteria or have a mutation that is identified by molecular genetic testing of the MMR genes.

Clinical diagnosis of LS: The Amsterdam II criteria define the minimum requirements for a clinical diagnosis of Lynch syndrome.

There should be at least three relatives with a Lynch/HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter or renal pelvis) *and* …

- One should be a first-degree relative to the other two
- At least two successive generations should be affected
- At least one should be diagnosed before age 50
- Familial adenomatous polyposis should be excluded
- Tumors should be verified by pathological examination

Inheritance
Autosomal dominant

Gene(s)
Mismatch repair genes
MLH1 & MSH2 (mutation present in about 90 percent of LS families)
MSH6 (mutation present in about 7–10 percent of LS families)
PMS2 (mutation present in <5 percent of LS families)

Non-mismatch repair genes
EPCAM (mutation present in 1–3 percent of LS families)

Genetic testing
Direct gene testing is available commercially. To identify colorectal cancer patients who may have LS, the current recommendations are to begin by ordering microsatellite instability (MSI) or immunohistochemistry (IHC) testing on the tumor sample. This can be performed by a pathologist on archived tumor blocks from a surgical specimen. These tests detect either an increased number of

microsatellite repeats (MSI, a hallmark of impaired mismatch repair gene activity), or the absence of the protein products of the mismatch repair genes (IHC). MSI/IHC have known utility for colorectal and endometrial cancers but are not routinely recommended for other cancers. If either test is positive, meaning that the mismatch repair genes appear to be impaired, then continue on to genetic testing that can determine which mismatch repair gene is mutated. Whenever possible, begin this genetic testing on an affected family member. The identification of a mutation confirms the diagnosis of LS. If a mutation is not identified, a diagnosis of LS can neither be confirmed nor ruled out; this result must be interpreted in the context of the patient's MSI/IHC results, family and personal history and test limitations. See "Overview of testing for Lynch syndrome tool" for more information.

Colon cancer risk			
	General population	Lynch syndrome	Mean age at cancer onset (LS)
Male	5.6%	28–75%*	44–61 years
Female	5.3%	24–52%*	44–61 years

*lower risks w/MSH6, PMS2 gene mutations

Associated cancer risks*			
Type of cancer	General population	Lynch syndrome	Mean age at cancer onset (LS)
Endometrium	2.7%	27–71%	46–62 years
Ovary	1.6%	3–13%	43 years
Other (stomach, hepatobilliary, urinary tract, etc.)	<1%	Stomach: 2–19% Urinary tract: 1–12% Others: 1–7%	Variable

*Increased risks for additional primary colon cancers

Non-cancer findings: keratoacanthomas, sebaceous adenomas

Screening recommendations (See "Screening guidelines tool"):

1. Colonoscopy: every one to two years starting at age 20–25 or two to five years prior to the earliest colon cancer in the family if diagnosed under age 25.
2. If colon cancer is found, consider removal of entire colon and continue annual screening for rectal cancer.
3. Consider prophylactic removal of the colon in cases where regular screening with colonoscopy cannot be performed.
4. Females: consider annual endometrial sampling and transvaginal ultrasound.
5. Consider prophylactic hysterectomy with bilateral salpingo-oophorectomy after childbearing is complete.
6. Consider annual urinalysis.
7. Consider EGD with extended duodenoscopy and polypectomy at two to three year intervals beginning at age 30.

Screening references:

NCCN Colorectal Cancer Screening Guidelines, V.2.2011.
nccn.org/professionals/physician_gls/f_guidelines.asp

ACG Guidelines for Colorectal Cancer Screening 2009.
http://s3.gi.org/physicians/guidelines/CCSJournalPublicationFebruary2009.pdf

Vasen, H., Watson, P., Mecklin, J.-P., & Lynch, H. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology*, 116(6), 1453–1456.

Inherited Thrombophilia Fact Sheet

Inherited thrombophilia is a genetic tendency toward venous thromboembolism (VTE) the usually presents in patients under age 50 and is often recurrent.

The most frequent causes are mutations of Factor V Leiden or prothrombin genes, which account for 50 to 60 percent of cases. Other defects in protein S, protein C, and antithrombin (i.e. antithrombin III) account for most of the rest.

About 50% of the VTE events in patients with inherited thrombophilia have an acquired risk factor, such as smoking, oral contraceptive use, recent surgery, or pregnancy.

Genetic causes of thrombophilia			
Mechanism/factor	**Population Prevalence**	**Inheritance Pattern**	**Risk of VTE by Age 60**
Deficiency of anticoagulants			
Antithrombin III	< 1%	Autosomal dominant	60%
Protein C	< 1%	Autosomal dominant	50%
Protein S	1%	Autosomal dominant	33%
Mechanism/factor	**Population Prevalence**	**Inheritance Pattern**	**Lifetime Risk of VTE**
Increased procoagulants			
Factor V Leiden	3-7%	Autosomal dominant	5-20%
Prothrombin G20210A	1-4%	Autosomal dominant	10-20%
Elevated homocysteine	10-15%	Multifactorial	Not yet determined

Adapted from Up To Date

Genetic Diagnostic Testing and Presymptomatic Testing

Genetic diagnostic testing is done when a patient is offered a genetic test based on symptoms and signs already present. The purpose is to rule out a genetic cause of current symptoms.

Presymptomatic testing is when an at-risk individual, who is asymptomatic at the time, carries a mutant gene that may increase the risk of developing disease at some point in the future. Typically, an effected family member has had a positive genetic diagnostic test.

"Red Flags" Suggesting Inherited Thrombophilia

Recurrent VTE, or spontaneous VTE
VTE at a young age
Recurrent miscarriage
Thrombosis in unusual sites (e.g. sagittal sinus) or multiple thrombi
Coronary or cerebral thrombosis at an early age (Men < 50, Women < 60)

Adapted from Genetics in the Physician Assistance's Practice