

## Importance of Family History in Gynecologic Cancer Prevention

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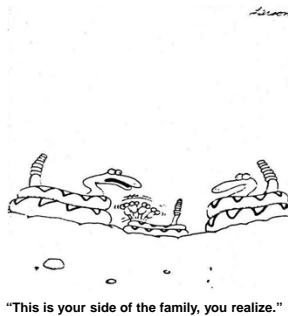
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### Objectives

- Introduce role of genetic counselor
- Discuss cancer genetics
- Explain differences between sporadic, familial, and hereditary cancers
- Explain importance of family history
- Discuss HBOC and Lynch Syndrome
- Discuss tools for your practice
- Discuss special issues



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### Genetic Counselors

- Genetic counselors are health professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling

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## Cancer Genetic Counselors- Roles

- ❑ Determine a patient's risk for a hereditary cancer susceptibility syndrome based on personal/family history
- ❑ Provide cancer risk assessment based on a patient's family history
- ❑ Determine what (if any) genetic tests are appropriate for a patient
- ❑ Discuss risks, benefits, and limitations of genetic testing
- ❑ Coordinate and interpret genetic tests
- ❑ Provide psychosocial counseling

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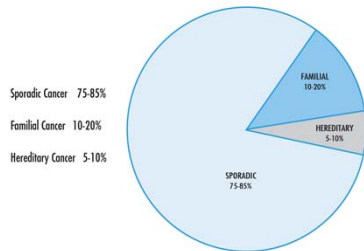
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Distribution of Sporadic, Familial, and Hereditary Cancer



Genes and Genetic Center

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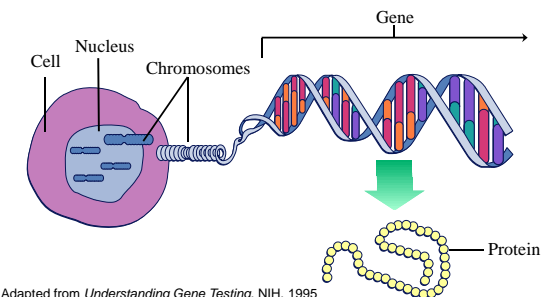
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## Chromosomes, DNA, and Genes



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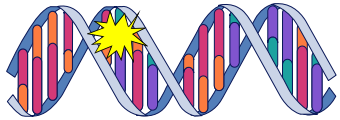
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## Disease-Associated Mutations

A **mutation** is a change in the normal base pair sequence



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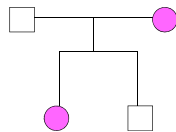
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## ALL CANCER IS GENETIC



BUT



NOT ALL CANCER IS HEREDITARY

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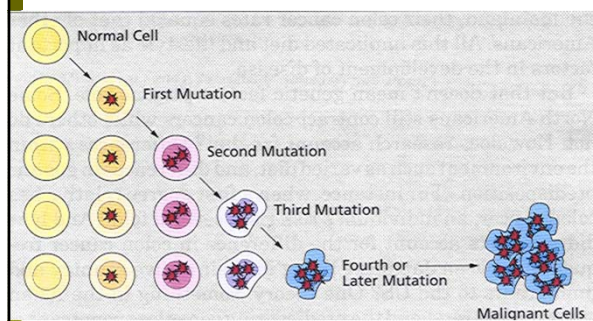
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Cancer results from the accumulation of mutations in cancer predisposing genes



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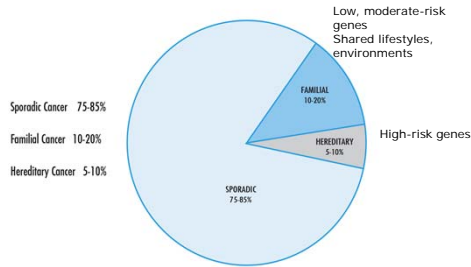
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#### Distribution of Sporadic, Familial, and Hereditary Cancer



### Hereditary Ovarian Cancer

- 20-25% of women with a diagnosis of ovarian cancer carry a hereditary gene mutation

Cancer J. 2012 Jul-Aug; 18(4):320-7.

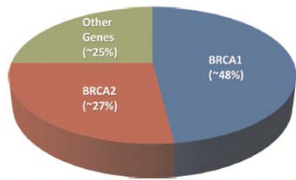


FIGURE 1. Genes responsible for hereditary ovarian cancer (including fallopian tube and primary peritoneal cancer). Other genes include *BRD1*, *BRP1*, *CHEK2*, *MRE11*, *MSH6*, *NBN*, *PAUS2*, *RAD50*, *RAD51C*, and *TP53*. Data derived from Walsh et al.<sup>8</sup>

### Hereditary Endometrial Cancer

- 5% of women with a diagnosis of uterine cancer carry a hereditary gene mutation
- 2-3% of women with endometrial cancer have Lynch syndrome

Histopathology 2013, 62, 2-30.  
Cancer J. 2012 Jul-Aug; 18(4):338-42.

## Importance of Identification

- Why is it important to identify hereditary gynecologic cancer predisposition syndromes in families?
  - High risk of cancer development
  - Early-onset cancers
  - Multiple organ systems may be involved
  - Increased risk for second primary cancer

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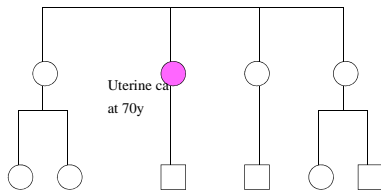
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## SPORADIC CANCER = FEW OCCURRENCES OF CANCER IN FAMILY



- Onset later in life
- Few relatives with cancer

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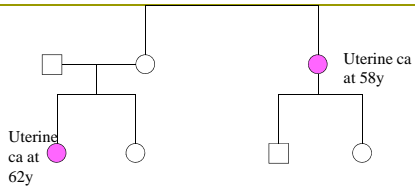
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## FAMILIAL CANCER = CLUSTER OF CANCER WITHIN FAMILIES



- Unclear inheritance pattern:
  - Chance alone
  - Common environment/lifestyle factors
  - Shared low, moderate-risk genes

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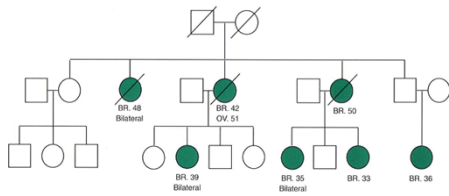
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## HEREDITARY CANCER



- ❑ Multiple affected individuals in multiple generations
- ❑ Early age of onset
- ❑ Individuals with multiple primaries
- ❑ Evidence of dominant inheritance
- ❑ Specific cancer clusters

## Family History Features Suggestive of a Hereditary Cancer Syndrome

- ❑ Multiple family members affected with cancer in multiple generations
- ❑ Early onset cancer (before age 50)
- ❑ Clustering of specific types of cancers
  - Breast and ovarian cancer in same family
  - Colon, uterine, and ovarian cancer in same family
- ❑ Individuals with more than one cancer
  - Breast and ovarian cancers in one person
- ❑ Rare cancers
  - Male breast cancer
- ❑ Ethnic background

## Hereditary Breast and Ovarian Cancer Syndrome

(HBOC)

## Hereditary Breast and Ovarian Cancer Syndrome

- BRCA1
  - Breast Cancer Gene 1
- BRCA2
  - Breast Cancer Gene 2

1/400-1/800 individuals in the general population carry a BRCA1 or BRCA2 mutation

Cancer J. 2012 Jul-Aug;18(4):320-7.

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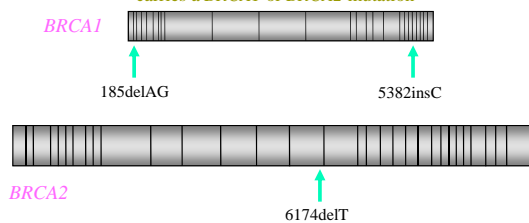
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## BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

An estimated 1 in 40 Ashkenazi Jews carries a BRCA1 or BRCA2 mutation



Cancer J. 2012 Jul-Aug;18(4):320-7.

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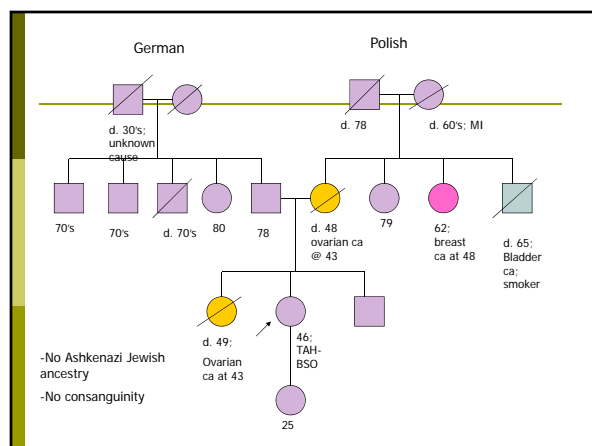
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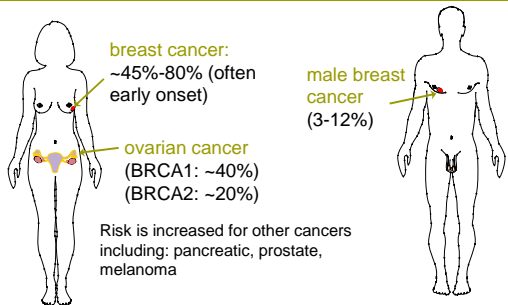
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## BRCA1/2-Associated Cancers: Lifetime Risks



Am J Hum Genet. 2003 Sep; 73(3):709.  
Cancer J. 2012 Jul-Aug; 18(4):320-7.

## Ovarian Cancer Risk Management Options

### □ Screening

- Concurrent transvaginal ultrasound and CA-125 every 6 months starting at age 30y or 5-10y earlier than first diagnosis of ovarian cancer in family
- Data suggests that screening is NOT effective for the early detection of ovarian tumors

J Med Genet 2009; 46: 593-597

## Ovarian Cancer Risk Management Options

### □ Risk Reduction- Surgery

- Bilateral salpingo-oophorectomy between ages 35y and 40y, or upon completion of childbearing, or individualized based on earliest onset of ovarian cancer in family
- 80-95% reduction in ovarian cancer risk in BRCA1/2 positive women following RRSO

NCCN Guidelines Version 1.2013 Hereditary  
Breast and/or Ovarian Cancer Syndrome  
N Engl J Med. 2002; 346(21):1616-1622.  
Cancer J. 2012 Jul-Aug; 18(4):320-7.

### Ovarian Cancer Risk Management Options

- ❑ Risk Reduction- Chemoprevention
  - Consider oral contraceptive use
- ❑ 50% reduction in ovarian cancer risk for BRCA1/2 positive women using oral contraceptives
  - Risk appears to decrease with longer period of use
  - Conflicting data regarding OCP use and breast cancer risk for BRCA carriers

N Engl J Med 1998; 339:424-428

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### Breast Cancer Risk Management Options

- ❑ Screening
  - Monthly BSE beginning at age 18y
  - Semi annual clinical breast exam beginning at age 25y
  - Annual mammogram and breast MRI beginning at age 25, or individualized based on earliest breast cancer onset in family
- ❑ Surgery
  - Discuss option of bilateral prophylactic mastectomy
- ❑ Chemoprevention
  - Tamoxifen/Raloxifene

NCCN Guidelines Version 1.2013  
Hereditary Breast and/or  
Ovarian Cancer Syndrome

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### Genetic Evaluation Guidelines

- ❑ Personal and/or family history:
  - Premenopausal breast cancer (<50y)
  - Triple negative breast cancer <60y
  - Bilateral breast cancer
  - Ovarian cancer
  - Male breast cancer
  - Postmenopausal breast cancer with additional relatives with breast cancer (especially if young age of onset)
  - Known hereditary cancer susceptibility syndrome

Adapted from: NCCN Guidelines  
Version 1.2013 Hereditary Breast  
and/or Ovarian Cancer Syndrome

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## Lynch Syndrome

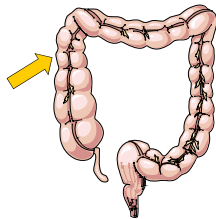
(HNPCC)

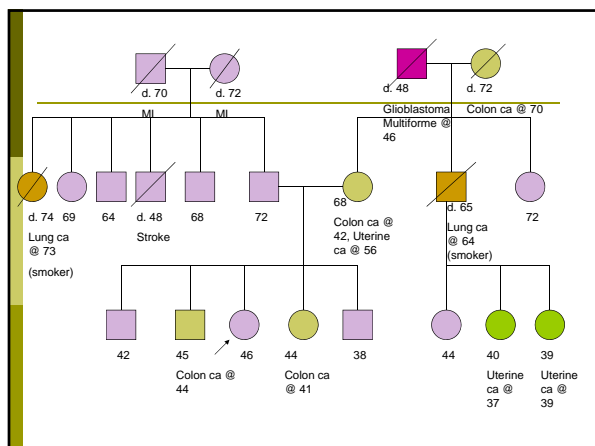
### Lynch syndrome

- ❑ MLH1
- ❑ MSH2
- ❑ MSH6
- ❑ PMS2
- ❑ EPCAM (TACSTD1)

### Features of Lynch Syndrome

- ❑ Early but variable age at CRC diagnosis (~45 years)
- ❑ Typically right-sided tumors
- ❑ Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors






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Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared to the General Population<sup>1</sup>

Cancer	General Population Risk	HNPCC	
		Risks	Mean Age of Onset
Colon	5.5%	80%	44 years
Endometrium	2.7%	20%-60%	46 years
Stomach	<1%	11%-19%	56 years
Ovary	1.6%	9%-12%	42.5 years
Hepatobiliary tract	<1%	2%-7%	Not reported
Urinary tract	<1%	4%-5%	~55 years
Small bowel	<1%	1%-4%	49 years
Brain/central nervous system	<1%	1%-3%	~50 years

NCCN Colorectal Cancer Screening Version 2.2012

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## Uterine/Ovarian Cancer Risk Management Options

- ▣ Screening
  - Annual office endometrial sampling is an option
  - Transvaginal ultrasound, CA-125
- ▣ There is no clear evidence to support screening for endometrial cancer in Lynch syndrome
- ▣ No evidence to support routine ovarian cancer screening

NCCN Colorectal Cancer Screening Version 2.2012

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## Uterine/Ovarian Cancer Risk Management Options

- ❑ Risk Reduction- Surgery
  - Prophylactic TAH-BSO should be considered after childbearing is complete
- ❑ Risk Reduction- Chemoprevention
  - Oral contraceptives reduce risk for endometrial and ovarian cancer in the general population, although efficacy in women with Lynch syndrome has not yet been determined

J. 2012 Jul-Aug; 18(4): 338-42

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## Management- Men and Women

- ❑ Colon cancer
  - Colonoscopy at age 20-25y or 2-5y prior to earliest CRC diagnosis in family, repeat every 1-2y
- ❑ Gastric and small bowel cancer
  - Consider EGD, with extended duodenoscopy and polypectomy at 2-3y intervals beginning at age 30-35
  - Consider capsule endoscopy for small bowel cancer at 2-3y intervals beginning at age 30-35
- ❑ Urothelial cancer
  - Consider annual urinalysis beginning at age 25-30y
- ❑ Pancreatic cancer
  - Limited data, no current guideline
  - High-risk programs: consider annual endoscopic ultrasound and MRI

NCCN Colorectal Cancer Screening Version 2.2012

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## Case Examples

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## Case 2

- ▣ Suspicion for LS is low
- ▣ No genetic testing for family indicated at this time
- ▣ Risk for gynecologic malignancies likely not increased over the general population risk

Tumor Testing <sup>a</sup>							
Immunohistochemistry (IHC)				MSI	BRAF V600E <sup>b</sup>	MLH1 Promoter Methylation	
MLH1	MSH2	MSH6	PMS2				
+	+	+	+	MSI-MSH2-Low	N/A	N/A	1) Sporadic cancer
+	+	+	+	MSI-High	N/A	N/A	1) Sporadic cancer
N/A	N/A	N/A	N/A	MSI-High	N/A	N/A	1) Sporadic cancer or germline mutation in any one of the known mismatch repair genes
-	+	+	-	N/A	N/A	N/A	1) Sporadic cancer 2) Germline mutation MLH1
-	+	+	-	N/A	Positive	N/A	1) Sporadic cancer
-	+	+	-	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline mutation MLH1 or constitutional MLH1 epimutation
-	+	+	-	N/A	Negative	Negative	1) Germline mutation MLH1 2) Germline mutation MSH2
+	-	-	+	N/A	N/A	N/A	1) Germline mutation MSH2 2) Germline mutation in TACSTD1, rarely germline mutation in MSH6
-	+	+	+	N/A	N/A	N/A	1) Germline mutation MLH1
+	+	+	-	N/A	N/A	N/A	1) Germline mutation PMS2 2) Germline mutation MLH1
+	-	+	+	N/A	N/A	N/A	1) Germline mutation MSH2
+	+	-	+	N/A	N/A	N/A	1) Germline mutation MSH6 2) Germline mutation MSH2

## Genetic Evaluation Guidelines

- ▣ Personal and/or family history of:
  - Colorectal cancer <50y
  - Endometrial cancer <50y
  - Colorectal and endometrial cancer in same individual
  - Ovarian cancer

## Family History

### Family History

- ❑ A genetic answer for the ovarian and/or endometrial cancer in a family is not always available
  - Undetectable mutation in known genes (BRCA1, BRCA2, MLH1, MSH2, etc.)
  - Mutation(s) in unidentified gene(s)
  - Affected family members not able to undergo testing
  - Cancer may be due to shared lifestyle/environmental factors, shared personal risk factors

### Family History

- ❑ Ovarian Cancer
  - Having one first-degree relative with ovarian cancer increases a women's risk to 1.5-4% risk
  - Having two affected relatives increases a women's risk to 7%
- ❑ Endometrial Cancer
  - Having one first-degree relative with endometrial cancer increases a women's risk 2-fold

Cancer Treat Res. 2010; 156: 69-85  
European Journal of Cancer Prevention 2009; 18:95-99.

## Family History

- Risk reducing surgery may be indicated for women with a strong family history
  - Definition for “strong family history” unclear
  - Recommendations for screening/prophylactic surgery provider-dependent

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## Family History- Tools For Your Practice

- Who?
  - Siblings, children, parents, aunts, uncles, grandparents, cousins
  - Maternal AND paternal relatives
  - Ancestry
- What?
  - Cancer type
  - Age of diagnosis
  - Unusual pathologic features
  - Multiple primaries

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## Family History- Tools For Your Practice

- Extremely important to gather family history for each patient and to develop a process that works well for your clinic
  - Paper screening forms
    - Physician or nurse directed questioning
  - Family history questionnaires in the electronic medical record
  - On-line tools
    - Surgeon General Family History Tool

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<https://familyhistory.hhs.gov/fhh-web/home.action>

## My Family Health Portrait

A tool from the Surgeon General

Using My Family Health Portrait you can:

- Enter your family health history.
- Print your family health history to share with family or your health care worker.
- Save your family health history so you can update it over time.

Talking with your health care worker about your family health history can help you stay healthy!

[Learn more about My Family Health Portrait](#)

Create a Family Health History

Use a Saved History

En Español

Em Português

In Italiano




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## Family History-Tools For Your Practice

- ❑ \*\*\*Family history changes over time\*\*\*
- ❑ Important to consider how a patient's family history will be updated and stored in your clinic

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## Special Issues




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## Insurance

- ❑ Genetic testing is expensive
- ❑ Varying coverage for genetic services from one insurance company to another
  - Most insurance companies cover genetic testing when medically necessary
- ❑ Some plans have direct exclusions to genetic testing
- ❑ Genetic counselors can help!

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## Genetic Discrimination- GINA

- ❑ Genetic Information Nondiscrimination Act of 2008 (GINA)
  - Health insurance
    - ❑ Prohibits use of genetic information in setting eligibility or premium or contribution amounts by group and individual health insurers
    - ❑ Prohibits health insurers from requesting or requiring an individual to take a genetic test
  - Employment
    - ❑ Prohibits use of genetic information by employers in making decisions regarding hiring, firing, and promoting
    - ❑ Prohibits employers from requesting, requiring, or purchasing genetic information about an individual employee or family member

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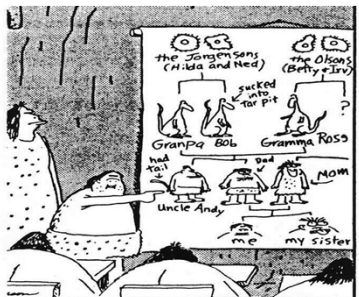
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## Questions?



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