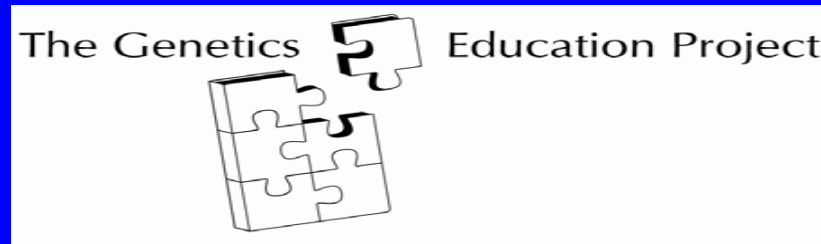


# Introduction to Cancer Genetics

Lori Van Manen, RN, MSc

## Acknowledgments:



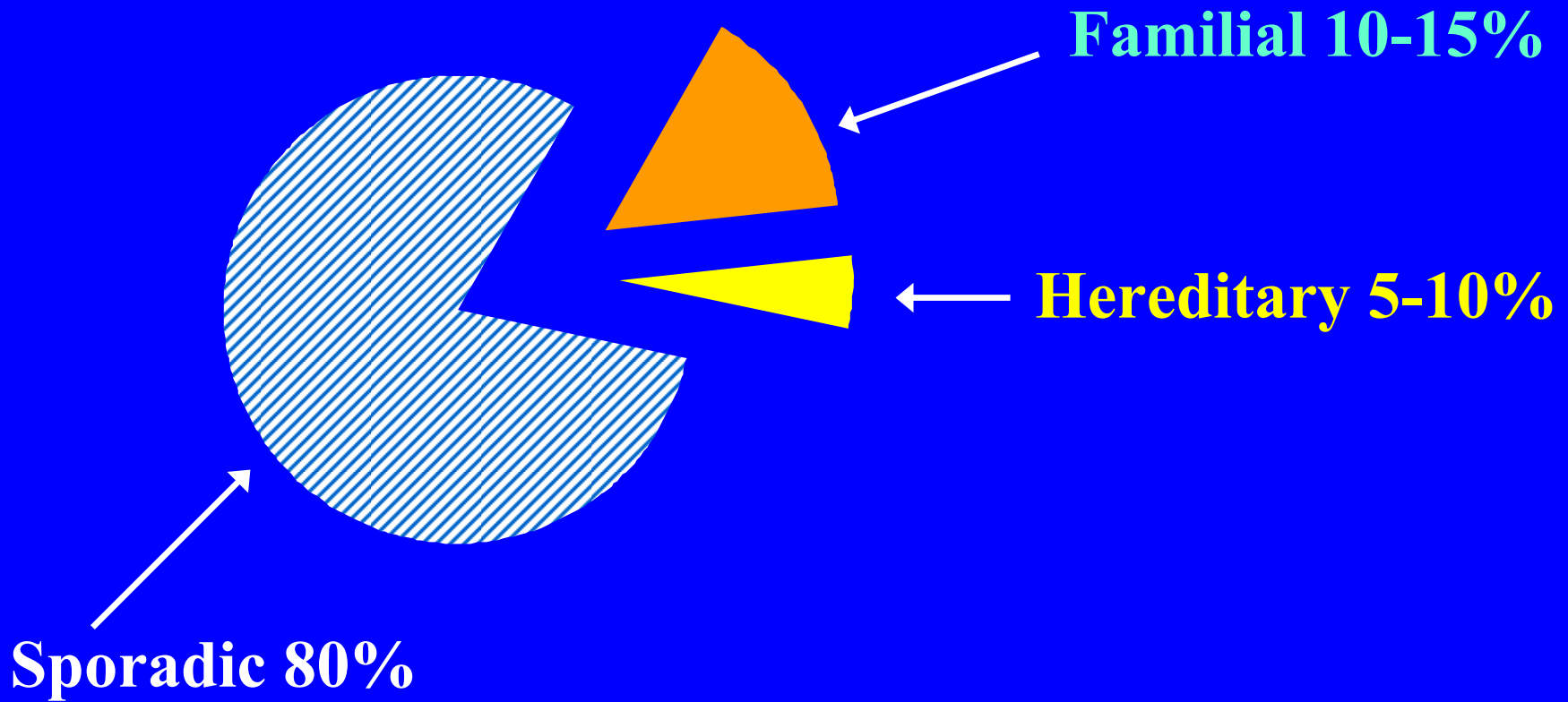
Project Funded by: Ontario Women's Health Council

Version: August 2005

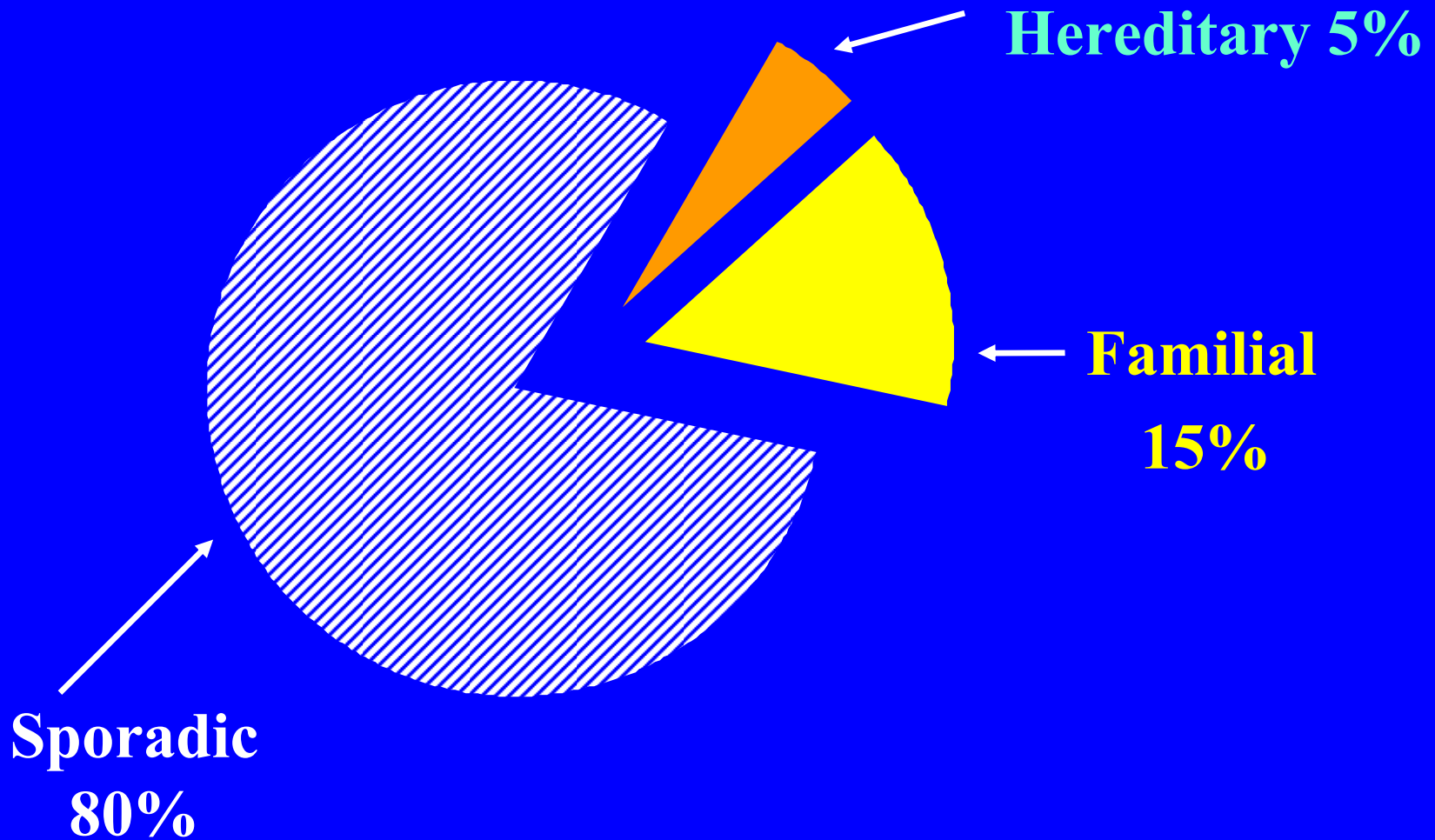
# Sporadic Vs Hereditary Cancer

- All cancer arises from changes in genes....
  - But NOT all cancer is inherited
- Most breast cancer and colon cancer is **sporadic** ~ **80%**
  - Due to mutations acquired over a person's lifetime
  - Cause unknown – multifactorial
    - age, environment, lifestyle (obesity, alcohol), chance, unknown factors
  - Generally has a later onset
- **Individuals with hereditary cancer have inherited a defect in a gene involved in the normal DNA repair mechanism**

# Proportion of Hereditary Breast Cancer



# Proportion of Hereditary Colorectal Cancer



## Compared to sporadic cancer hereditary cancer has...

- A higher risk of developing cancer
- A younger age of onset
  - Generally < 50 years of age
- Multiple primary cancers
- Less common than in the general population

# Genes involved in hereditary breast/ovarian cancer

- *BRCA1*- chromosome 17 and
- *BRCA2* - chromosome 13 >2,600 mutations
- Autosomal dominant transmission
- Carrier frequency of *BRCA1* & 2 mutations

# Inherited Colorectal Cancer

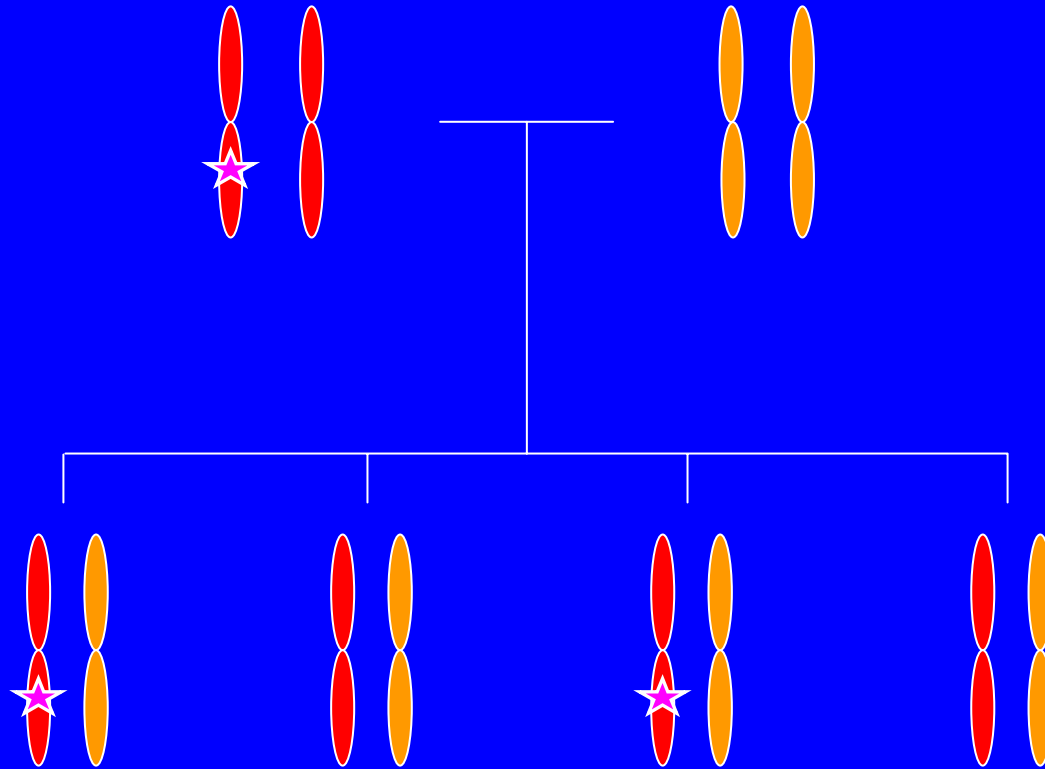
Two common syndromes:

- **Hereditary Non-Polyposis Colon Cancer (HNPCC)**
  - ~2 - 5% of colorectal cancer
  - Incidence 1 in 200 - 2,000
- **Familial Adenomatous Polyposis (FAP)**
  - <1% of colorectal cancer
  - Incidence of 1 in 8,000 – 14,000
- Autosomal dominant inheritance

# Hereditary Non-Polyposis Colon Cancer

- HNPPC is genetically heterogeneous
  - 5 genes:
    - *MLH1* & *MSH2* (most common), *MSH6*, *PMS1* & *PMS2*
- High penetrance
- Characterized by:
  - Earlier onset than sporadic cancer
  - More aggressive, proximal, right sided tumours
  - Risk for extra-colonic tumours

# Autosomal Dominant Inheritance



★ = Gene Change

# Consequences of having a *BRCA* mutation

	Estimated Risk in <i>BRCA</i> Mutation Carriers – by Age 70	In General Population
Breast Cancer ♀	50 - 85%	11%
Ovarian Cancer <i>BRCA1</i>	40-60%	1-2%
Ovarian Cancer <i>BRCA2</i>	10-20%	1-2%
Breast Cancer ♂ <i>BRCA2</i>	6%	<1%

## Cancer Risk in Individuals with HNPCC to Age 70 Compared to the General Population

<b>Cancer</b>	<b>General Population Risk</b>	<b>HNPCC Risk</b>	<b>Mean Age of Onset n HNPCC</b>
<b>Colon</b>	7 %	70-80%	45 years
<b>Endometrium</b>	2.3%	20-60%	46 years
<b>Stomach</b>	<1%	13-19%	56 years
<b>Ovary</b>	1.5%	9-12%	42.5 years
<b>Hepatobiliary tract</b>	<1%	2-7%	54 years
<b>Urinary tract</b>	<1%	4-5%	~55 years
<b>Small Bowel</b>	<1%	1-2%	49 years
<b>Brain / CNS</b>	<1%	1-4%	50 years

# Who should be offered referral for genetic counselling and/or genetic testing for hereditary breast cancer?....

- Multiple cases of breast and/or ovarian cancer in family
  - closely related relatives
  - more than one generation
  - Breast cancer diagnosed at < age 50
- Breast cancer diagnosed at age < 35
- Family member with both breast and ovarian cancers
- Ashkenazi Jewish + relatives with breast or ovarian cancer



## ... Who should be offered referral for genetic counselling and/or genetic testing for hereditary breast cancer?

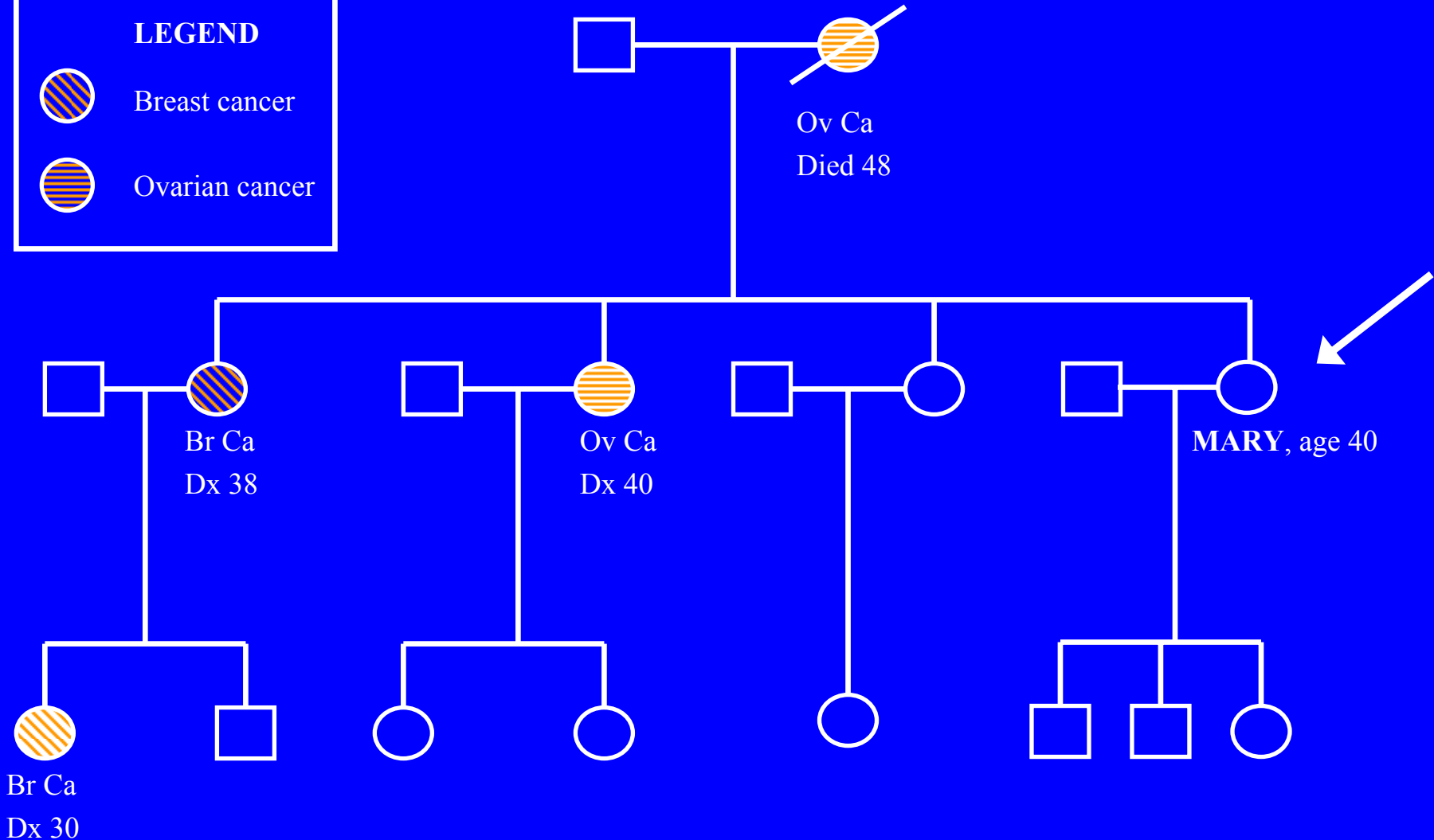
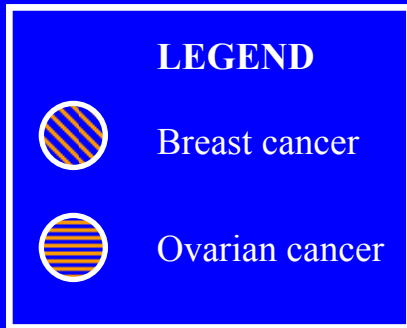
- Family member with primary cancer in both breasts
  - especially if diagnosed < age 50
- Family member with invasive serous ovarian cancer
- Male breast cancer
- Family member with an identified with a *BRCA1* or *BRCA2* mutation



# Case: Mary

- Mary - healthy 40 year old
  - Concerned about her risk for cancer
  - Family history of both breast & ovarian cancer

# Case: Mary's family history



Mary was referred to genetics...  
A genetics consultation involves:

- Detailed family history information
- Pedigree documentation
  - Confirmation of cancer history: pathology reports/death certificates
- Medical & exposure history
- Empiric risk assessment
- Hereditary cancer / genetic risk assessment
- Psychological assessment

# ...A genetics consultation involves:

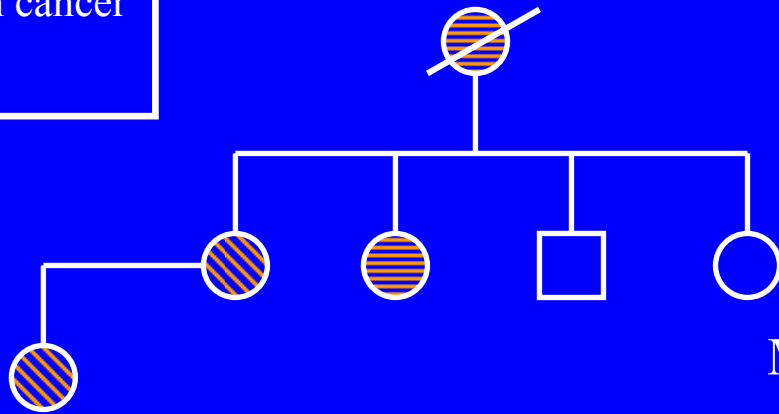
- Assessment of eligibility for genetic testing
  - Estimated risk of a mutation must be  $\geq 10\%$
  - Availability of living affected relative to be tested first
- Discussion of risks, benefits & limitations of test
- Testing and disclosure of genetic test results
  - May be months before results are available
- Determining patient's thoughts about breast cancer
  - Motivations for testing
- Screening/management recommendations

Legend

 Breast cancer

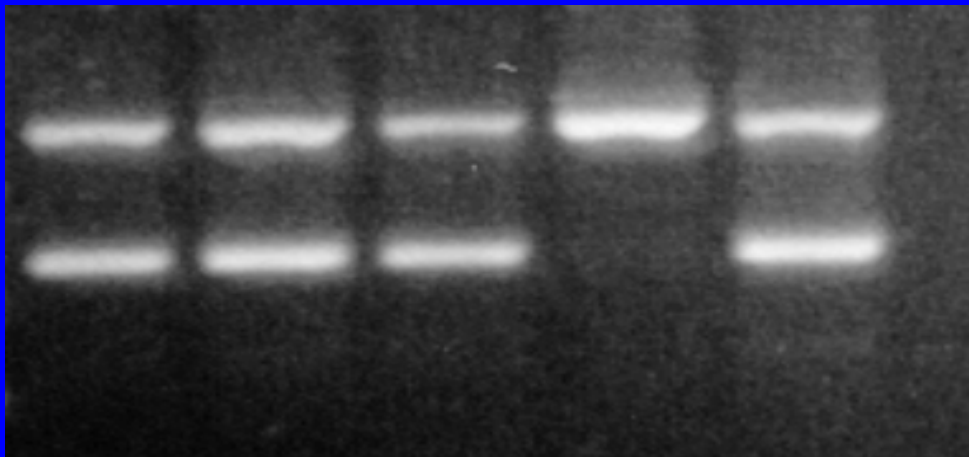
 Ovarian cancer

# Case: Mary's test results....



Mary

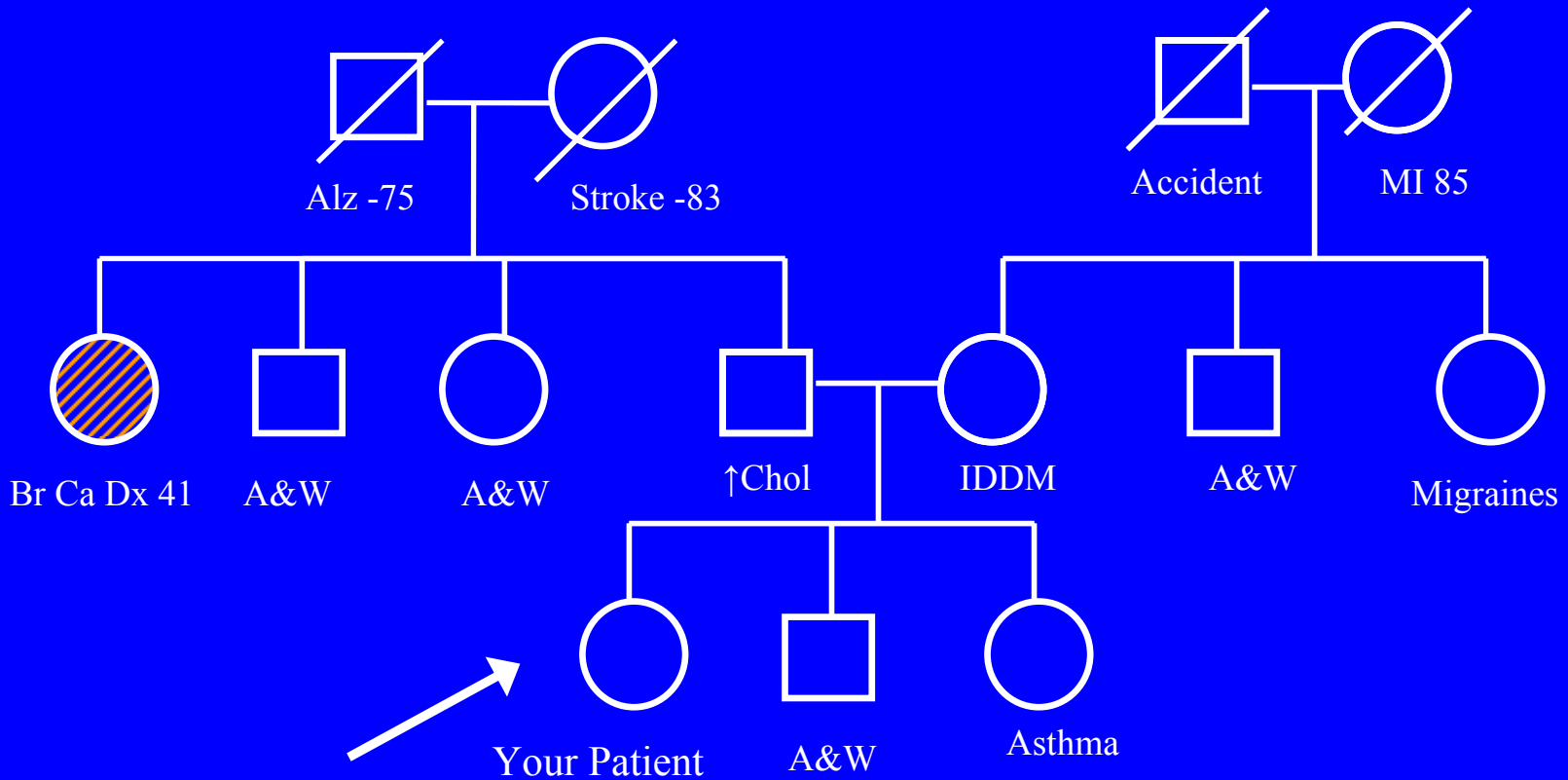
*BRCA1* 185delAG



--- Normal

--- Mutation

# Example 2

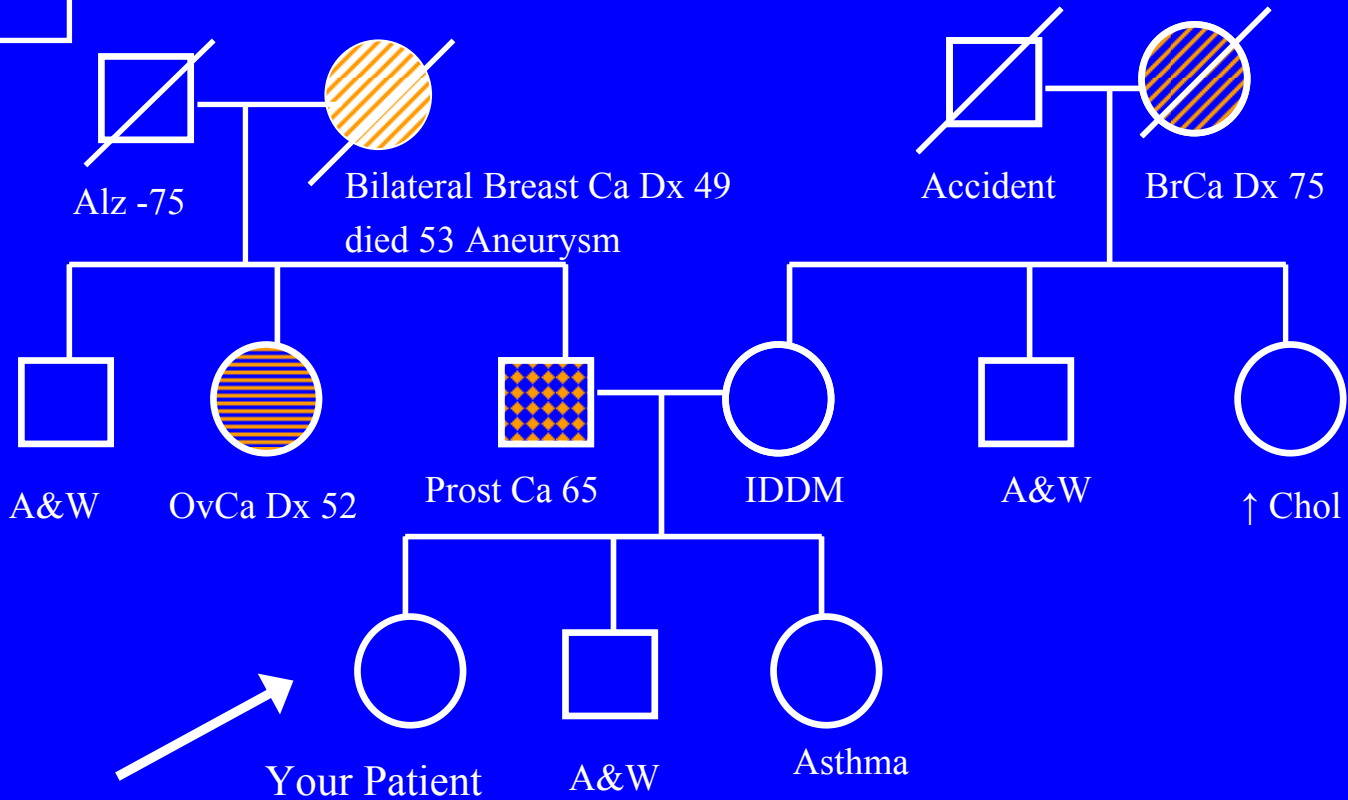
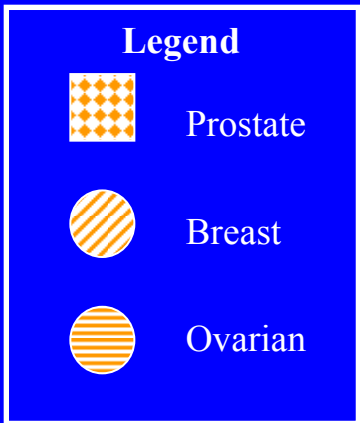


# Example 2

Answer:

- **Moderate** risk for hereditary breast cancer
- One 1<sup>st</sup>/2<sup>nd</sup> degree relative with breast cancer at 35-49 years
- Management:
  - CBE and mammogram q1 years starting at 40
  - Discuss lifestyle changes
  - Consider enrollment in chemoprevention clinical trials

# Example 3



# Example 3

Answer:

- **High** risk for hereditary breast/ovarian cancer
- Two relatives on the same side of the family with breast cancer <50 or ovarian cancer (any age)
- One 1<sup>st</sup>/2<sup>nd</sup> degree relative with breast cancer:
  - <35 years
  - Bilateral, first before age 50
  - Breast and ovarian cancer (any age)
  - Male breast cancer

## Example 3

Answer: **High** risk

- Management:
  - Offer genetics or familial cancer clinic referral
  - Pt. agrees:** Familial Cancer Clinic will suggest management
  - Pt. declines:** Discuss management with familial cancer clinic or manage as moderate risk
- Consider chemoprevention, i.e. Tamoxifen
- Referral to psychologist and/or support group
- Discuss: lifestyle changes, enrollment in chemoprevention clinical trials

# Who should be offered referral for genetic counselling and/or genetic testing for hereditary colon cancer?

- Multiple cases in family with HNPCC spectrum of cancers with at least 1 relative with CRC or endometrial CA
- CRC at < 35 years
- Multiple HNPCC cancers in one family member
- Family member with FAP or >10 adenomatous polyps
- Family member with known mutation
- Family member with colonic adenoma or cancer with high microsatellite instability

\*\*\*Not all who are referred will have genetic testing\*\*\*

# Who should be offered genetic testing?

## Amsterdam Criteria

### “3-2-1 rule”

- Three relatives with colon cancer, two being first-degree relatives of the third
- Two generations affected with colon cancer
- One colon cancer patient with diagnosis age  $\leq 50$ 
  - One is a first degree relative of the other two





\*There are more detailed criteria - this is a quick guide

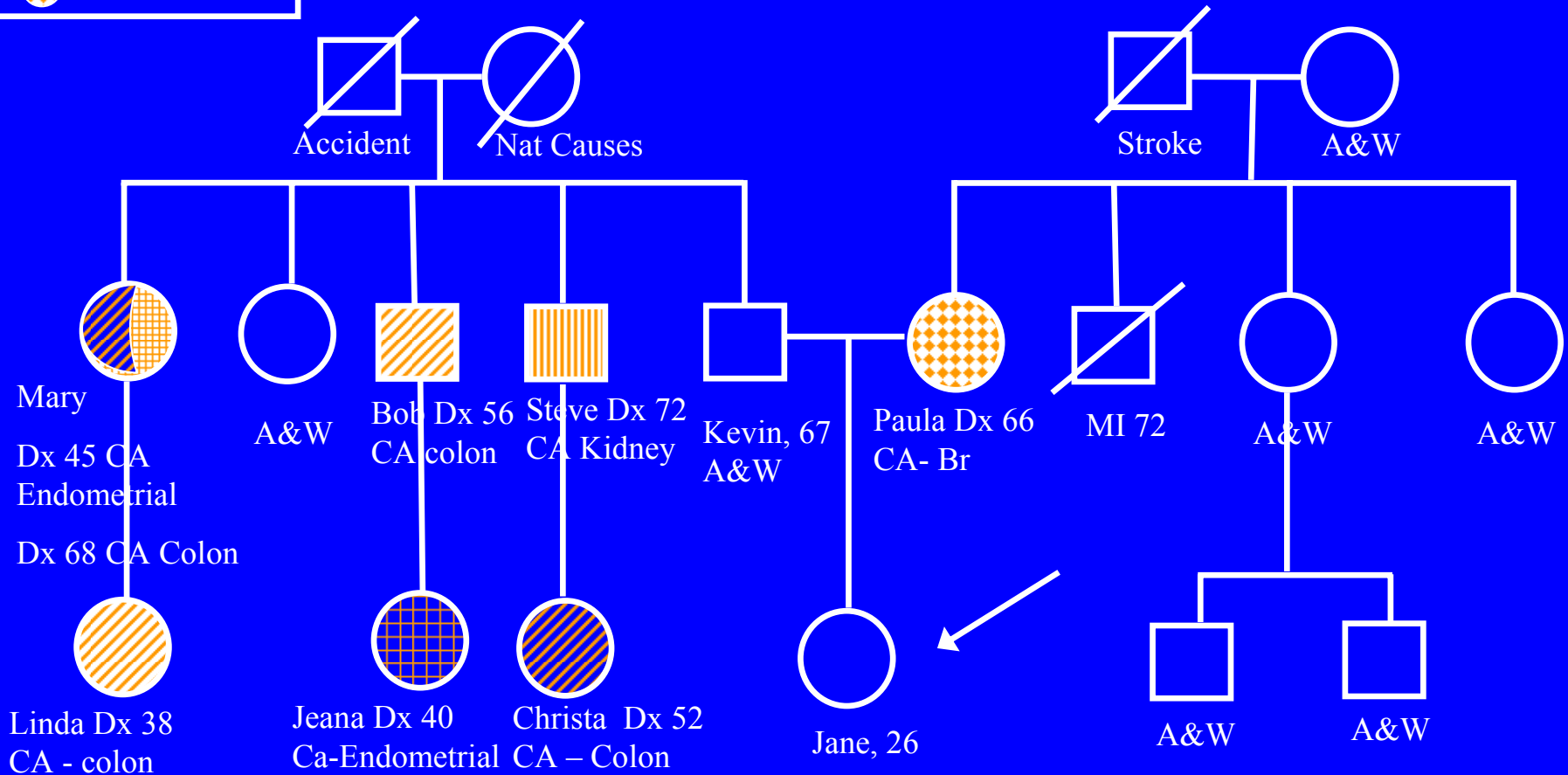
# Case

- Jane - healthy 26 y.o.
- Office visit for a routine pap smear and renewal of birth control pills
- History:
  - Any cancer in the family?
    - Mother with breast cancer at 66

# Jane's Family Pedigree

## LEGEND

-  Kidney
-  Colon
-  Endometrial
-  Breast



# Recommendations for Jane's family

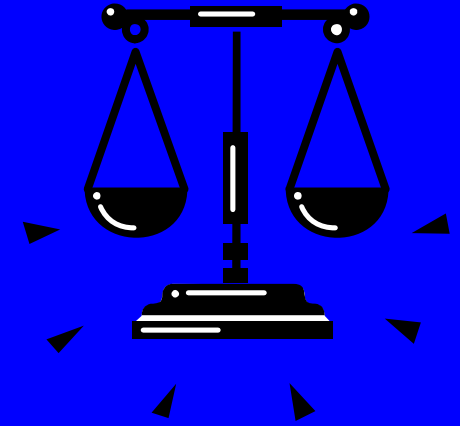
- Jane's paternal family history is suggestive of HNPCC.
- Jane was asked to discuss genetic testing with her family members diagnosed with cancer.
- Appropriate to test an affected member first.
- If a mutation found in one of the HNPCC genes then sequential testing of the family can be performed.

# Results from Genetic Testing

- **Positive**
  - Deleterious mutation identified
- **Negative**
  - Interpretation differs if a mutation has previously been identified in the family
    - Mutation known – true negative
    - Mutation unknown – uninformative
- **Variant of unknown significance**
  - Significance will depend on how variant tracks through family, i.e. is variant present in people with disease?
  - Can use software to predict functional significance
  - Check with lab: ? reported previously

# Risks/Benefits/Limitations of genetic testing

## Positive test result



### Potential Benefits:

- Clinical intervention may improve outcome
- Family members at risk can be identified
- Positive health behaviour can be reinforced
- Reduction of uncertainty

### Potential Risks:

- Adverse psychological reaction
- Family issues/distress
- Uncertainty -incomplete penetrance
- Insurance/job discrimination
- Confidentiality issues
- Intervention may carry risk

# Risks/Benefits/Limitations of genetic testing?

## Negative test result



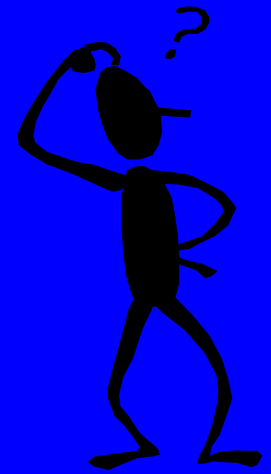
### Potential Benefits:

- Avoidance of unnecessary clinical interventions
- Emotional - relief
- Children can be reassured
- May avoid higher insurance premiums

### Potential Risks:

- Adverse psychological reaction (i.e. survivor guilt)
- Dysfunctional family dynamics
- Complacent attitude to health

# Risks/Benefits/Limitations of genetic testing?



## Uninformative test result

### Potential Benefits:

- Future research may clarify test results
- Importance of positive health behaviour can be reinforced
- Some relief
- Higher insurance premiums may be avoided

### Potential Risks:

- Continue clinical inventions which may carry risks
- Complacent attitude to health
- Uncertainty
- Continued anxiety
- Higher insurance premiums may not be reduced

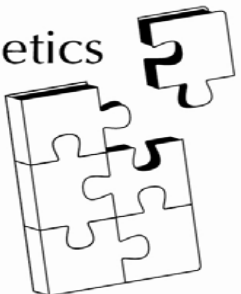
# Resources

- The National Cancer Institute:  
<http://cancernet.nci.nih.gov/>
  - Detailed information on cancer for patients and physicians including causes, treatments, clinical trials & more
- Canadian Cancer Society: [www.cancer.ca](http://www.cancer.ca)
- FORCE: [www.facingourrisk.org](http://www.facingourrisk.org)
- [www.hereditarybreastcancer.cancer.ca](http://www.hereditarybreastcancer.cancer.ca)
  - Patient information aid
- Gene Clinics
  - See Gene Reviews for clinical summaries[www.Genetests.org](http://www.Genetests.org)

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The Genetics Education Project

A 3D illustration of a puzzle with one piece missing. The puzzle is shown in a perspective view, with the missing piece floating above it. The puzzle is composed of several interlocking pieces, and the missing piece is a single piece that fits into the top-right corner of the puzzle. The puzzle is rendered in a simple, black-and-white line-art style.

