CANCER EDUCATION DAYS

Genetic Markers: Ovarian and Uterine Cancer

Sarah Muir, CGC

October 13, 2023

WINDSOR REGIONAL HOSPITAL

OUTSTANDING CARE – NO EXCEPTIONS!

Presenter Disclosure

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  - Advisory Boards: N/A

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Objectives

- Review the main concepts of hereditary cancer
- Review hereditary syndromes relating to gynecological cancers
- Review the provincial genetic testing criteria
- Introduce the regional cancer genetics program and how to refer

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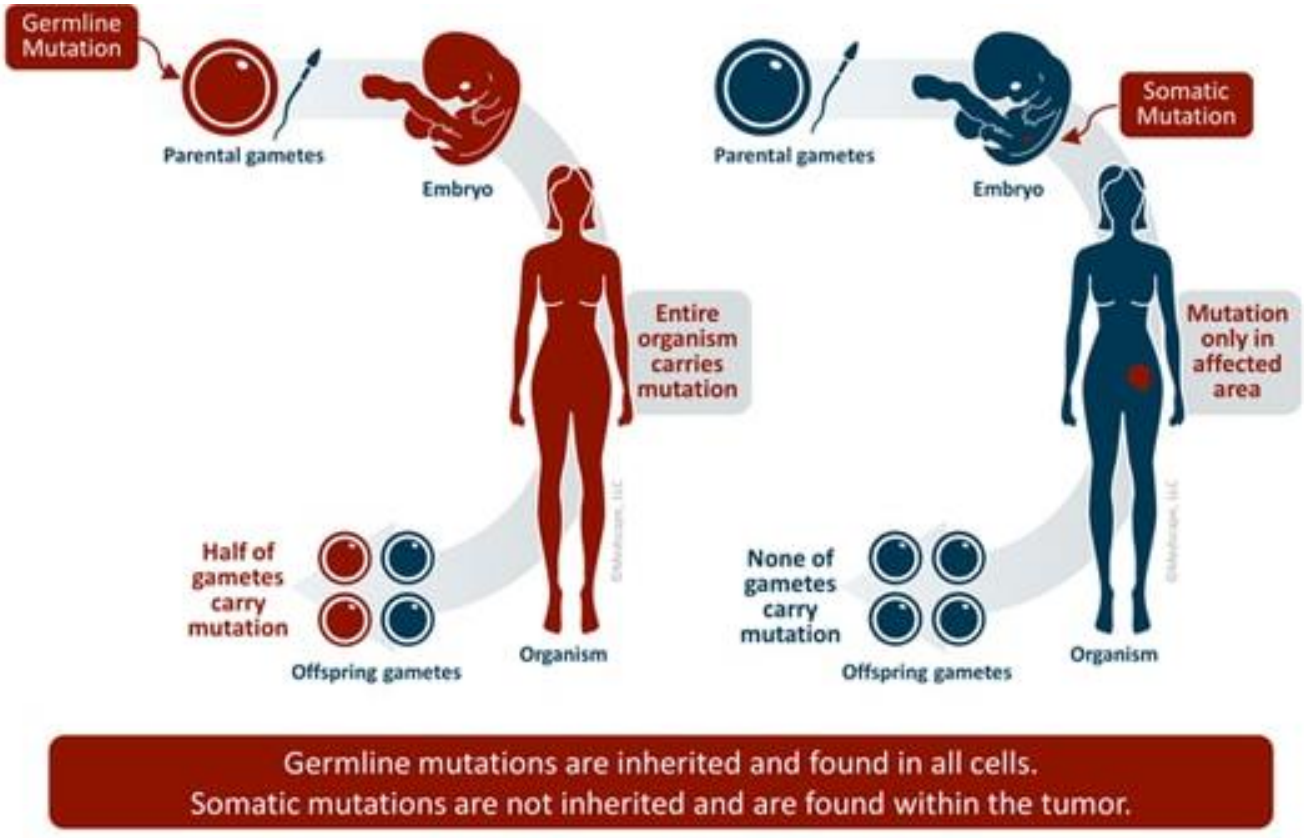
Concepts in Hereditary Cancer

- All cancer is *genetic*, not all cancer is *hereditary*
  - Accumulation of DNA damage in cells
  - Somatic vs. germline testing



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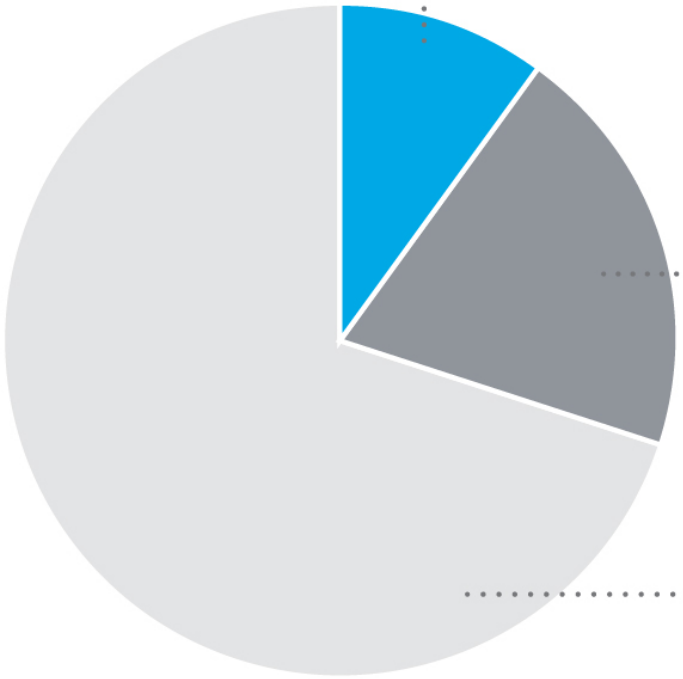
Concepts in Hereditary Cancer



HEREDITARY CANCER

A clustering of cancer in a family due to inherited gene changes (mutations), which can be passed from parent to child

FAMILIAL CANCER

A clustering of cancer in a family that may be due to genes and/or other shared factors, such as environment and lifestyle

SPORADIC CANCER

Happens by chance in one or two related family members, typically at older ages

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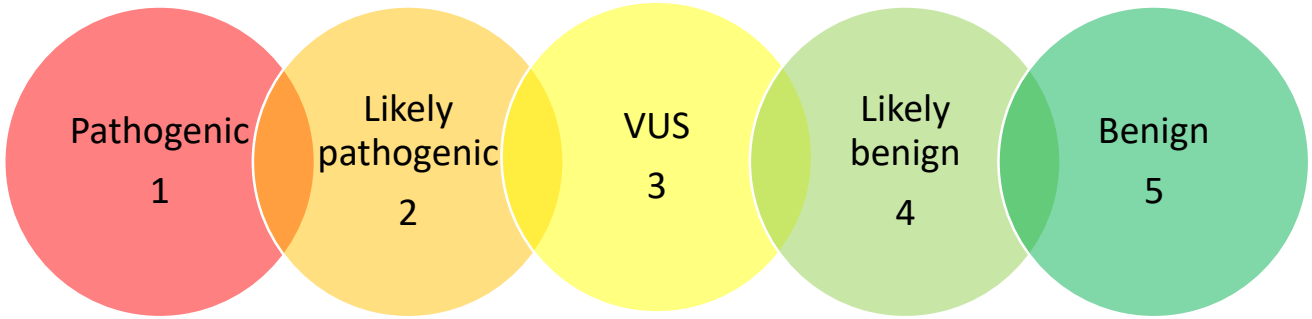
Concepts in Hereditary Cancer

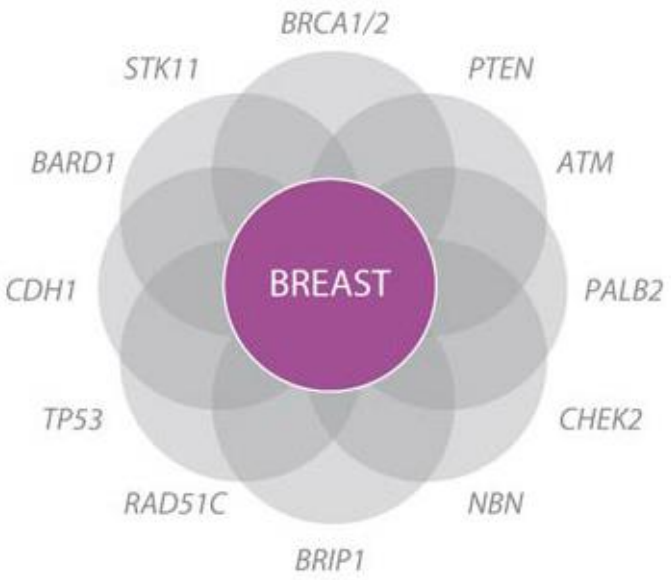
- Hereditary cancer = *pathogenic/likely pathogenic* germline DNA variants
  - Not all variants are BAD



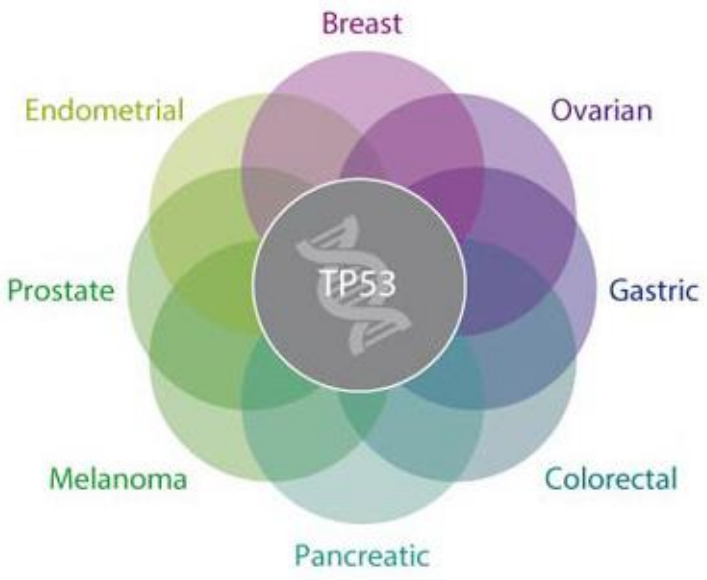
Abbreviations:
VUS – Variant of uncertain significance

Concepts in Hereditary Cancer

Genetic Overlap



Multiple genes can increase the risk of a single cancer



Multiple cancers can be associated with a single gene

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When to think GENETICS!

- Gynecological Cancers
  - Cervical
  - Vaginal
  - Vulvar
  - Ovarian ✓
  - Uterine ✓

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Lynch Syndrome *(MLH1, MSH2, MSH6, PMS2, EPCAM*)*

AKA hereditary non-polyposis colorectal cancer (HNPCC) syndrome

- Affects 1 in 279
- Lynch syndrome-related cancers include:
  - Colorectal
  - Endometrial *(13 – 57 % risk)*
  - Gastric
  - Gastroesophageal junction
  - Ovarian *(3 – 38 % risk)*
  - Pancreatic
  - Ureter and renal pelvis
  - Biliary tract
  - Brain
  - Small bowel
  - Sebaceous adenomas

- **Genetic Testing Criteria**
  - IHC-deficient tumour (exception sebaceous neoplasm)
    - BRAF/MLH1 promoter methylation normal
  - IHC-deficient sebaceous neoplasm + ≥1 of: ≤60y, multiple, ≥1 close relative with LS cancer
  - Affected individual/unaffected FDR from family who meets <u>all</u> of:
    - ≥3 relatives with LS cancers
    - ≥2 successive generations
    - ≥1 diagnosed <50y
    - 1 case in a FDR of other 2

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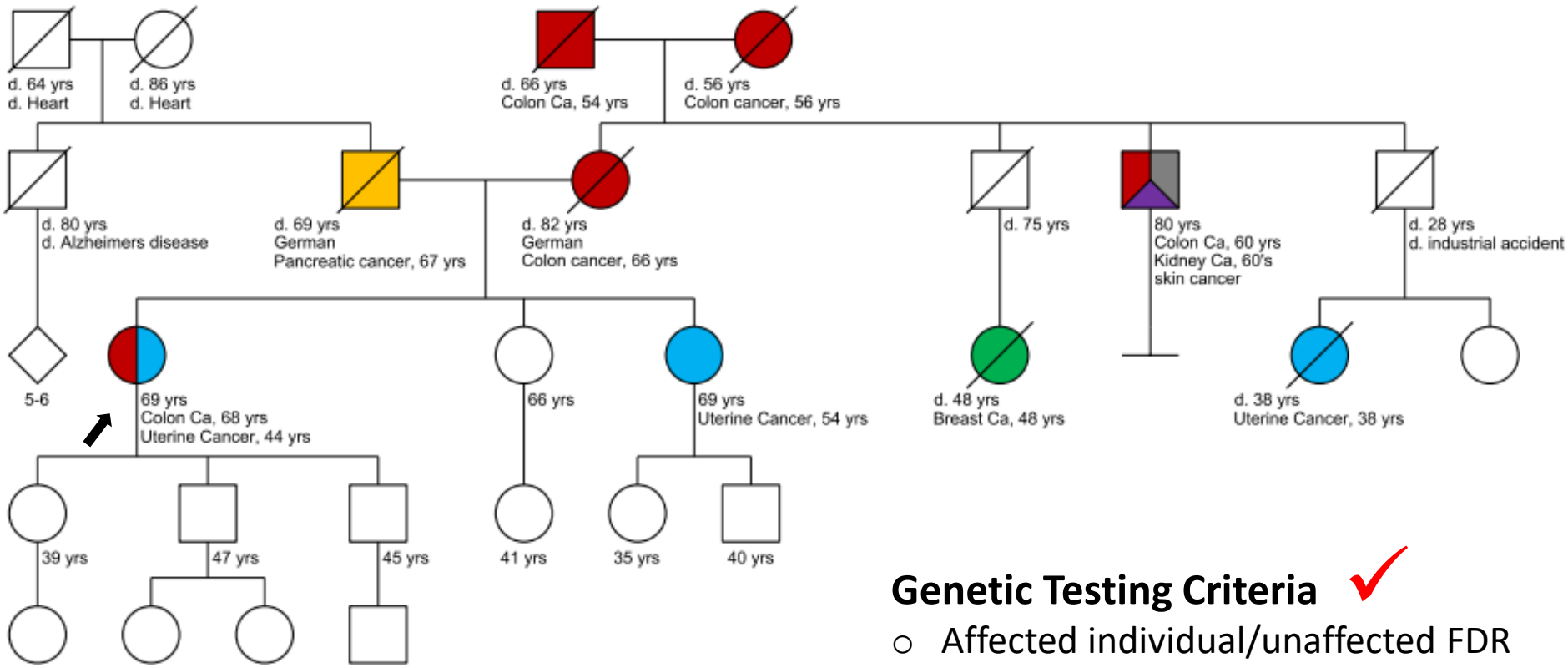
Abbreviations:
IHC – Immunohistochemistry, LS – Lynch syndrome, FDR – first degree relative

NCCN Guidelines Genetic/Familial High-Risk Assessment: Colorectal V1.2023

Case Example



Genetic Testing Criteria ✓

- Affected individual/unaffected FDR from family who meets <u>all</u> of:
  - ≥3 relatives with LS cancers
  - ≥2 successive generations
  - ≥1 diagnosed <50y
  - 1 case in a FDR of other 2

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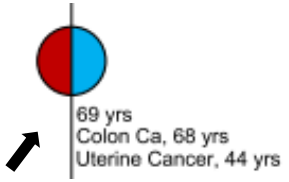
Case Example



Microscopic Description

Colon and Rectum Biomarker Results

Mismatch Repair

Immunohistochemistry (IHC) Testing for Mismatch Repair (MMR) Proteins: Background nonneoplastic tissue / internal control with intact nuclear expression

IHC Interpretation: Loss of nuclear expression of MSH2 and MSH6: high probability of Lynch syndrome (sequencing and / or large deletion / duplication testing of germline MSH2 may be indicated and, if negative, sequencing and / or large deletion / duplication testing of germline MSH6 may be indicated)

Reporting Note: There are exceptions to the above IHC interpretations. These results should not be considered in isolation, and clinical correlation with genetic counseling is recommended to assess the need for germline testing.

MLH1 Result: Intact nuclear expression

MSH2 Result: Loss of nuclear expression

MSH6 Result: Loss of nuclear expression

Genetic Testing Criteria ✓

- IHC-deficient tumour (exception sebaceous neoplasm)
  - BRAF/MLH1 promoter methylation normal

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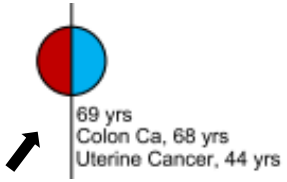
Case Example



Germline Genetic Testing

DNA FINDING:

Gene	Transcript	Exon	Variant	Prediction	Zygosity	Interpretation
MSH2	NM_000251.3	15	***	***	Heterozygous	Pathogenic

INTERPRETATION: Detected. DNA sequencing of the coding region of *MSH2* exon 15 identified the targeted variant described above.

This individual is at increased lifetime risk for *MSH2* associated cancers due to the above variant.

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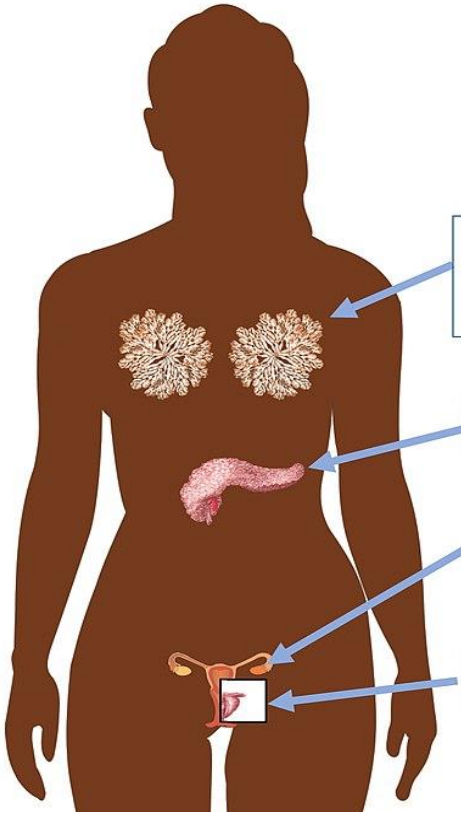
Hereditary Breast and Ovarian Cancer (HBOC) Syndrome



	BRCA1	BRCA2
Breast cancer:	>60% Males up to 1.2%	>60% Males 2-7%
Pancreas cancer:	≤5%	5-10%
Ovarian cancer:	39-58%	13-29%
Prostate cancer:	7-26%	19-61%

- Affects 1 in 400

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Kuchenbaecker KB et al, JAMA 2017; 317:2402-2416; NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V1.2024

Hereditary Breast and Ovarian Cancer (HBOC) Syndrome

Genetic Testing Criteria

- Breast cancer ≤45y
- Breast cancer ≤50y with limited family structure
- Breast cancer ≤50y with second primary breast cancer
- Triple negative invasive breast cancer ≤60y
- Male breast cancer, any age
- **Invasive epithelial ovarian cancer*, epithelial fallopian tube or peritoneal cancer (any age)**

  *Includes serous, endometriod, mixed, clear cell, mucinous and poorly differentiated
- Breast cancer + family history of ≥1 of: breast cancer ≤50y, triple negative breast cancer ≤60y, ovarian cancer, male breast cancer, high risk prostate cancer, pancreatic cancer, or ≥2 additional breast/prostate cancer cases

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“Other” genes

- Ovarian *(2 – 20 % risk)*
  - *ATM*
  - *BRIP1*
  - *PALB2*
  - *RAD51C*
  - *RAD51D*
- Uterine
  - *PTEN* – syndromic
  - *POLD1* - *limited evidence*
  - POLE - *limited evidence*
  - *BRCA1/2* *(serous endometrioid type, limited evidence)*
- Rare
  - uterine sarcomas, small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) - *SMARCA4/SMARCB1* genes

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NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V. 1.2024

Genetic Testing: Uterine & Ovarian

- OH-CCO Provincial Hereditary Cancer Testing (HCT) Program for adults
  - Multidisciplinary working-group
  - Standardized Gene List (Panels)

☐ **Hereditary Gastrointestinal Panel**
(Includes Lynch Syndrome, Gastric, Pancreatic and Polyposis Panels)
APC, ATM, BMPR1A, BRCA1, BRCA2, CDH1, CDKN2A, CHEK2, CTNNA1, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, SDHB, SDHD, SMAD4, STK11, TP53

☐ **Hereditary Lynch Syndrome Panel**
EPCAM, MLH1, MSH2, MSH6, PMS2
IHC results:

☐ **Hereditary Breast/Ovarian/Prostate Panel**
ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

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Erie St. Clair Regional Cancer Program

- Established in 2013 to increase access to cancer genetics services in the ESC LHIN
  - Phone appointments during and after business hours (8am-4pm)

- Medical Genetics affiliation LHSC
  - Geneticist supported

Sarah Muir
Genetic Counsellor (full time)

Elana Wishnefsky
Genetic Counsellor (part time)

Dr. Victoria Mok Siu
Medical Geneticist

How to Refer

- Fax a referral form

* Included in Cancer Education Day Supplementary Resource Package

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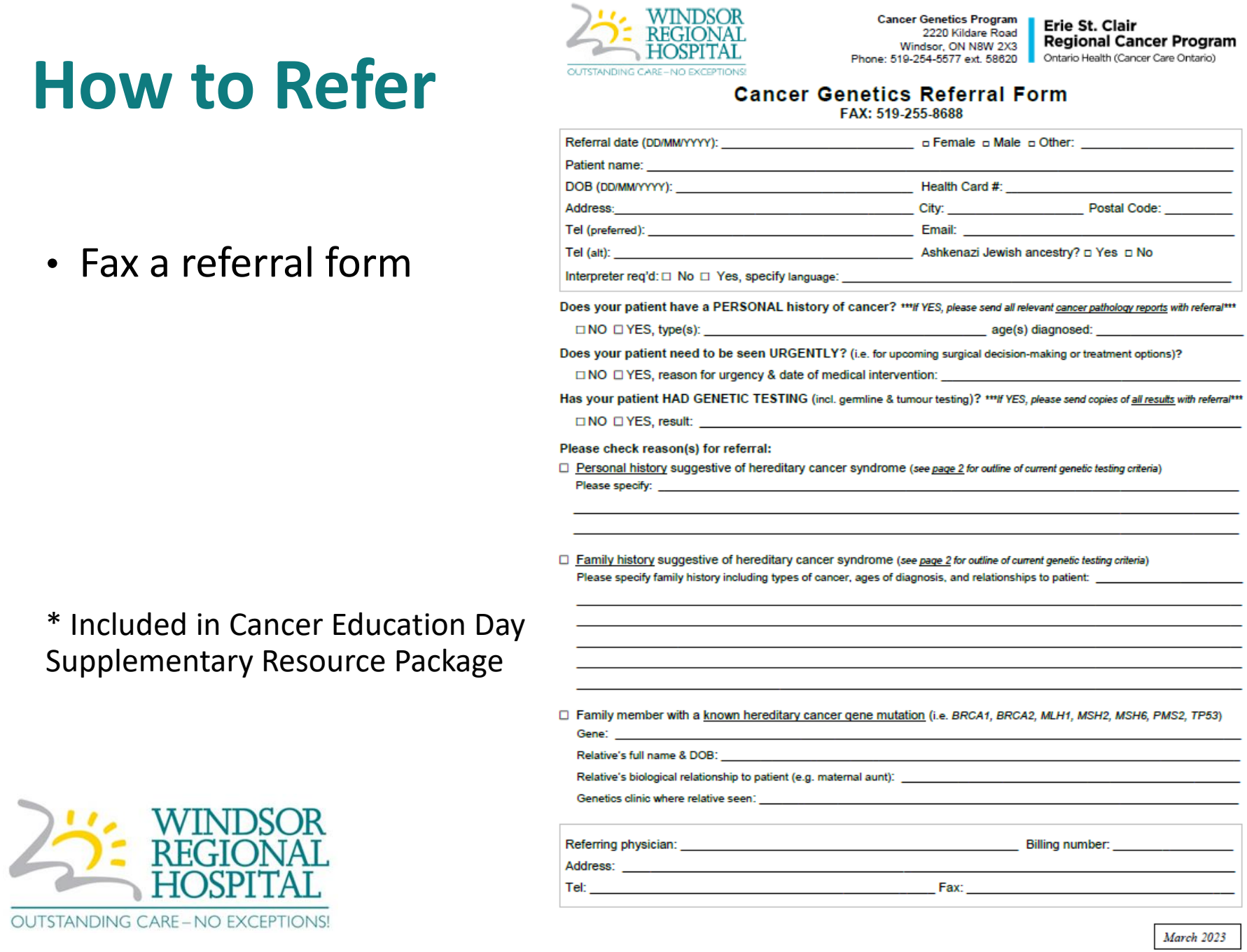

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Cancer Genetics Program
2220 Kildare Road
Windsor, ON N8W 2X3
Phone: 519-254-5577 ext. 58620

Erie St. Clair Regional Cancer Program
Ontario Health (Cancer Care Ontario)

Cancer Genetics Referral Form

FAX: 519-255-8688

Referral date (DD/MM/YYYY): _____ ◻ Female ◻ Male ◻ Other: _____

Patient name: _____

DOB (DD/MM/YYYY): _____ Health Card #: _____

Address: _____ City: _____ Postal Code: _____

Tel (preferred): _____ Email: _____

Tel (alt): _____ Ashkenazi Jewish ancestry? ◻ Yes ◻ No

Interpreter req'd: ☐ No ☐ Yes, specify language: _____

Does your patient have a PERSONAL history of cancer? ***If YES, please send all relevant cancer pathology reports with referral***

☐ NO ☐ YES, type(s): _____ age(s) diagnosed: _____

Does your patient need to be seen URGENTLY? (i.e. for upcoming surgical decision-making or treatment options)?

☐ NO ☐ YES, reason for urgency & date of medical intervention: _____

Has your patient HAD GENETIC TESTING (incl. germline & tumour testing)? ***If YES, please send copies of all results with referral***

☐ NO ☐ YES, result: _____

Please check reason(s) for referral:

☐ Personal history suggestive of hereditary cancer syndrome (*see page 2 for outline of current genetic testing criteria*)

Please specify: _____

☐ Family history suggestive of hereditary cancer syndrome (*see page 2 for outline of current genetic testing criteria*)

Please specify family history including types of cancer, ages of diagnosis, and relationships to patient: _____

☐ Family member with a known hereditary cancer gene mutation (i.e. *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, TP53*)

Gene: _____

Relative's full name & DOB: _____

Relative's biological relationship to patient (e.g. maternal aunt): _____

Genetics clinic where relative seen: _____

Referring physician: _____ Billing number: _____

Address: _____

Tel: _____ Fax: _____

March 2023

High Risk Ontario Breast Screening Program (HR-OBSP)

- Individuals with a personal or family history of epithelial ovarian cancer may also be eligible for an assessment for the High Risk Ontario Breast Screening Program (HR-OBSP).
- Fax a referral form

* Included in Cancer Education Day Supplementary Resource Package

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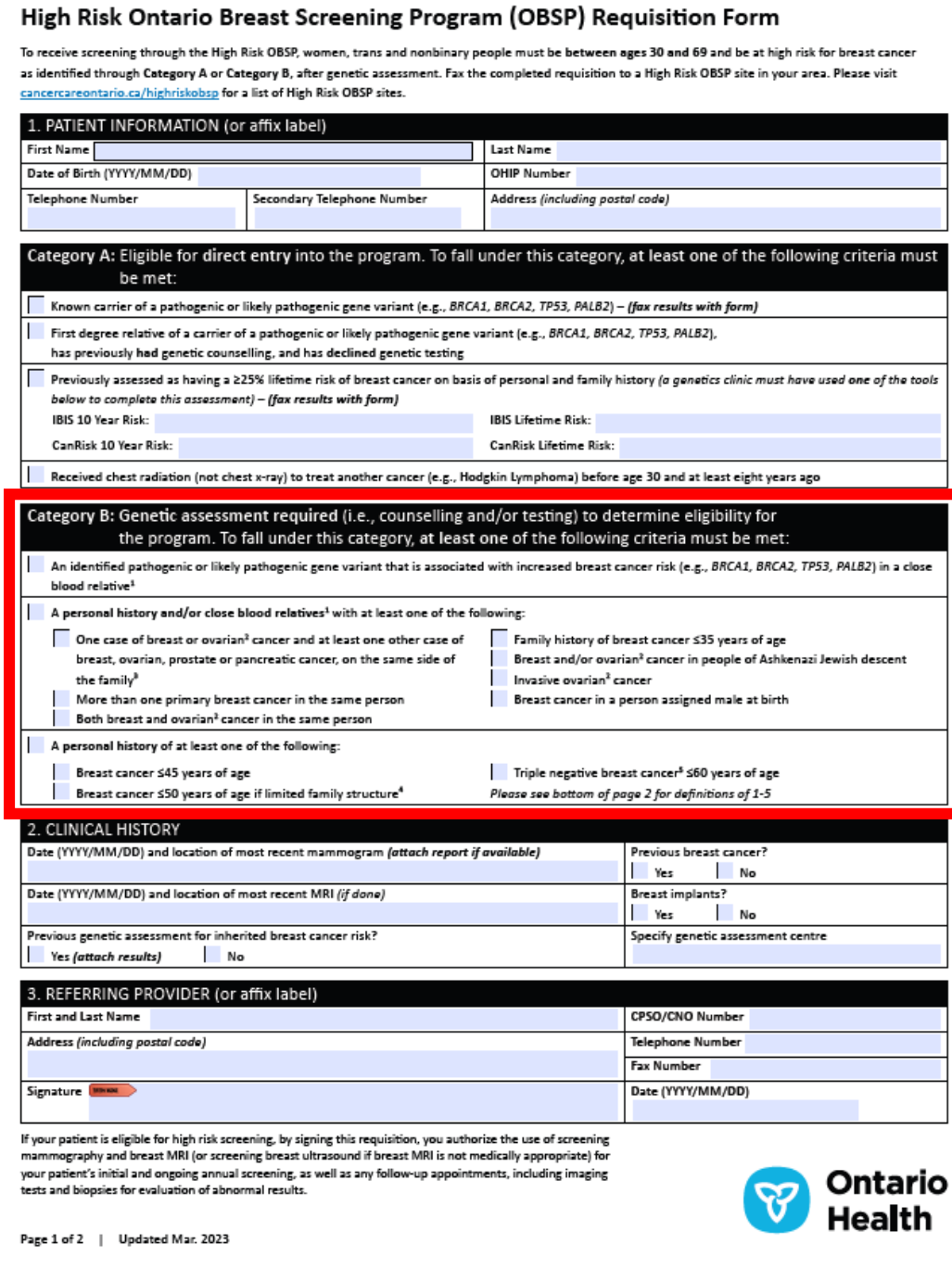

High Risk Ontario Breast Screening Program (OBSP) Requisition Form

To receive screening through the High Risk OBSP, women, trans and nonbinary people must be **between ages 30 and 69** and be at high risk for breast cancer as identified through **Category A** or **Category B**, after genetic assessment. Fax the completed requisition to a High Risk OBSP site in your area. Please visit cancercareontario.ca/highriskobsp for a list of High Risk OBSP sites.

1. PATIENT INFORMATION (or affix label)

First Name		Last Name
Date of Birth (YYYY/MM/DD)		OHIP Number
Telephone Number	Secondary Telephone Number	Address *(including postal code)*

Category A: Eligible for **direct entry** into the program. To fall under this category, **at least one** of the following criteria must be met:

- ☐ Known carrier of a pathogenic or likely pathogenic gene variant (e.g., *BRCA1, BRCA2, TP53, PALB2*) – ***(fax results with form)***
- ☐ First degree relative of a carrier of a pathogenic or likely pathogenic gene variant (e.g., *BRCA1, BRCA2, TP53, PALB2*), has previously **had** genetic counselling, and has **declined** genetic testing
- ☐ Previously assessed as having a ≥25% lifetime risk of breast cancer on basis of personal and family history *(a genetics clinic must have used one of the tools below to complete this assessment)* – ***(fax results with form)***
  - IBIS 10 Year Risk: | IBIS Lifetime Risk:
  - CanRisk 10 Year Risk: | CanRisk Lifetime Risk:
- ☐ Received chest radiation (not chest x-ray) to treat another cancer (e.g., Hodgkin Lymphoma) before age 30 and at least eight years ago

Category B: **Genetic assessment required** (i.e., counselling and/or testing) to determine eligibility for the program. To fall under this category, **at least one** of the following criteria must be met:

- ☐ An identified pathogenic or likely pathogenic gene variant that is associated with increased breast cancer risk (e.g., *BRCA1, BRCA2, TP53, PALB2*) in a close blood relative[1]
- ☐ **A personal history and/or close blood relatives[1] with at least one of the following:**
  - ☐ One case of breast or ovarian[2] cancer and at least one other case of breast, ovarian, prostate or pancreatic cancer, on the same side of the family[3]
  - ☐ More than one primary breast cancer in the same person
  - ☐ Both breast and ovarian[2] cancer in the same person
  - ☐ Family history of breast cancer ≤35 years of age
  - ☐ Breast and/or ovarian[2] cancer in people of Ashkenazi Jewish descent
  - ☐ Invasive ovarian[2] cancer
  - ☐ Breast cancer in a person assigned male at birth
- ☐ **A personal history** of at least one of the following:
  - ☐ Breast cancer ≤45 years of age
  - ☐ Breast cancer ≤50 years of age if limited family structure[4]
  - ☐ Triple negative breast cancer[5] ≤60 years of age

Please see bottom of page 2 for definitions of 1-5

2. CLINICAL HISTORY

Date (YYYY/MM/DD) and location of most recent mammogram ***(attach report if available)***	Previous breast cancer? ☐ Yes ☐ No
Date (YYYY/MM/DD) and location of most recent MRI *(if done)*	Breast implants? ☐ Yes ☐ No
Previous genetic assessment for inherited breast cancer risk? ☐ Yes ***(attach results)*** ☐ No	Specify genetic assessment centre

3. REFERRING PROVIDER (or affix label)

First and Last Name	CPSO/CNO Number
Address *(including postal code)*	Telephone Number
	Fax Number
Signature	Date (YYYY/MM/DD)

If your patient is eligible for high risk screening, by signing this requisition, you authorize the use of screening mammography and breast MRI (or screening breast ultrasound if breast MRI is not medically appropriate) for your patient's initial and ongoing annual screening, as well as any follow-up appointments, including imaging tests and biopsies for evaluation of abnormal results.

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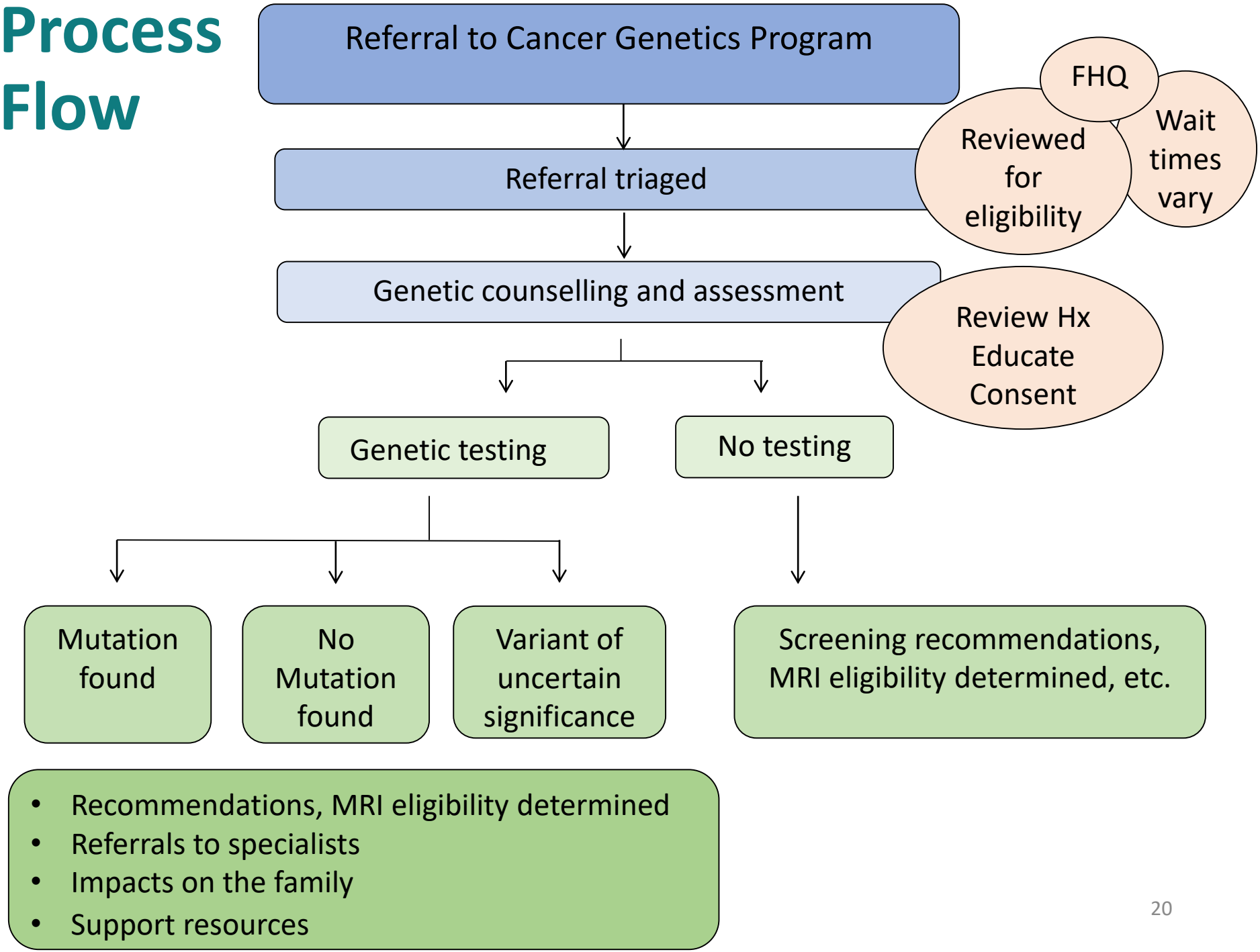
Ontario Health

Process Flow



Case Example

Referral to Cancer Genetics Program

- 35 yo female
- Personal history ovarian high grade serous carcinoma dx 34
- Family history of breast cancer

Referral triaged

FHQ

- Sent FHQ
- Eligible for genetic testing

Reviewed for eligibility

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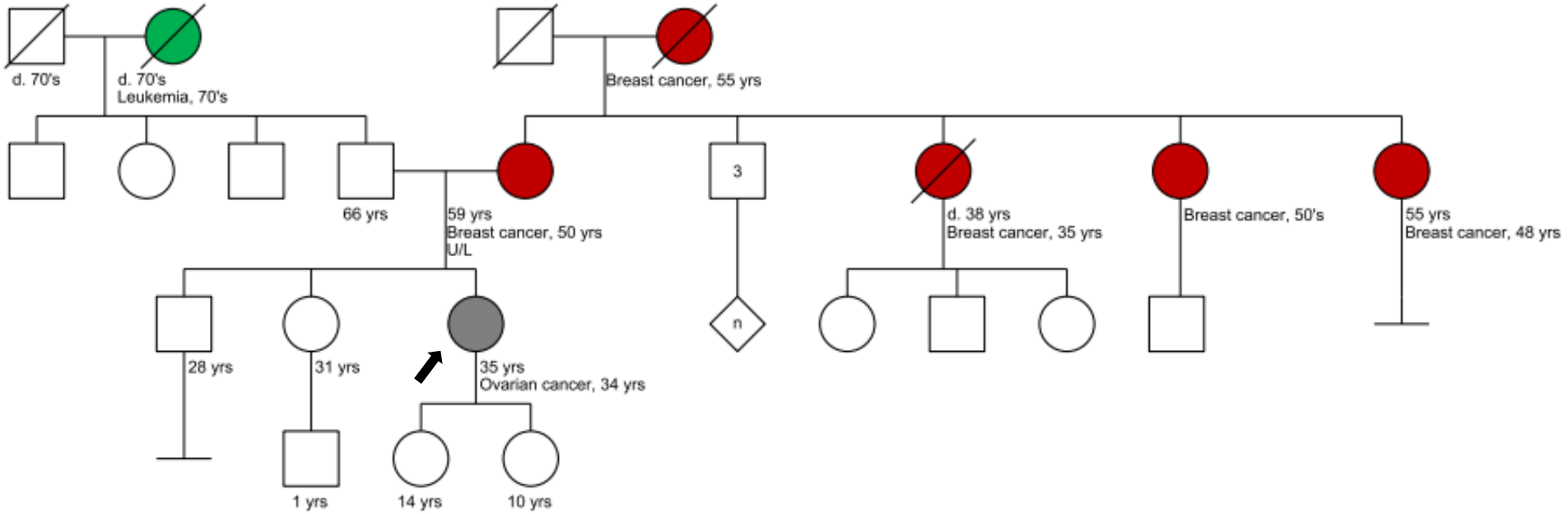
Case Example

Genetic counselling and assessment



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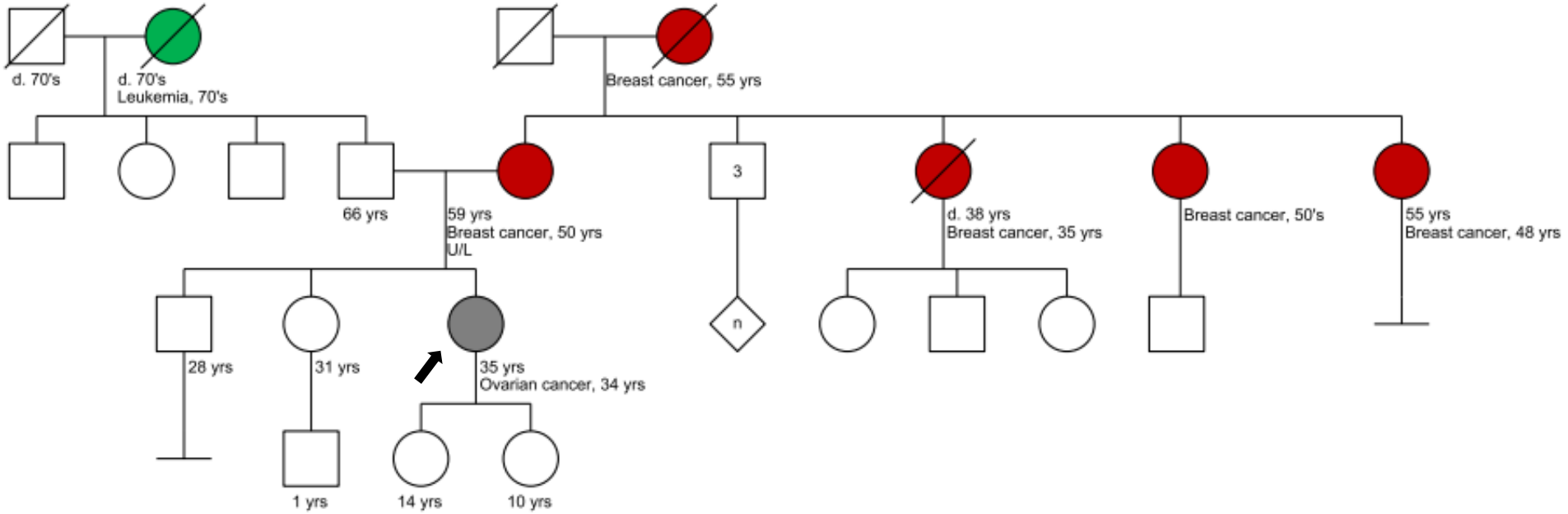
Case Example

Genetic counselling and assessment

Genetic testing



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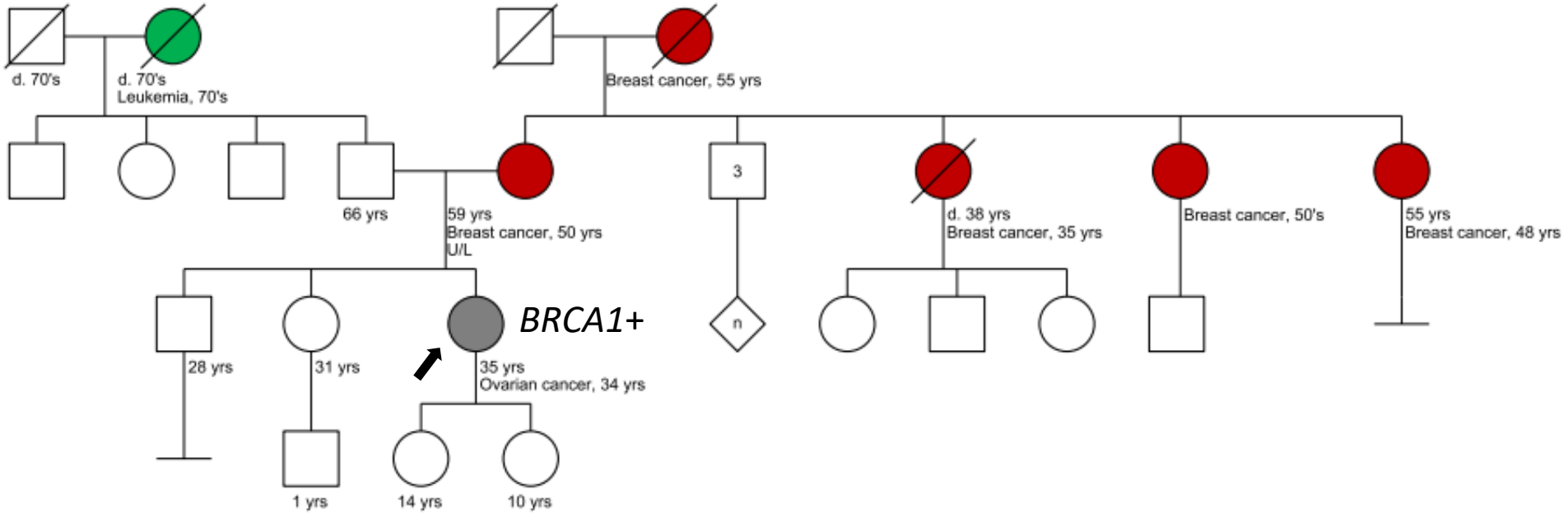
Case Example

Genetic counselling and assessment

Genetic testing

Mutation found



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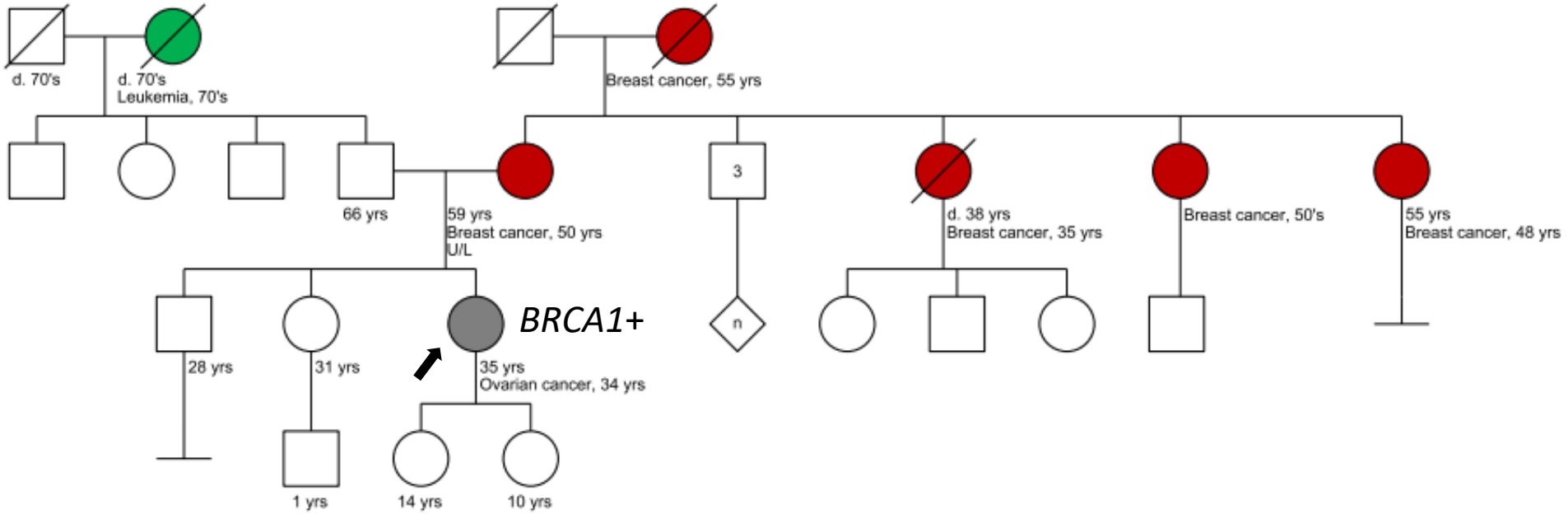
Case Example

- Recommendations, MRI eligibility determined
- Referrals to specialists
- Impacts on the family
- Support resources



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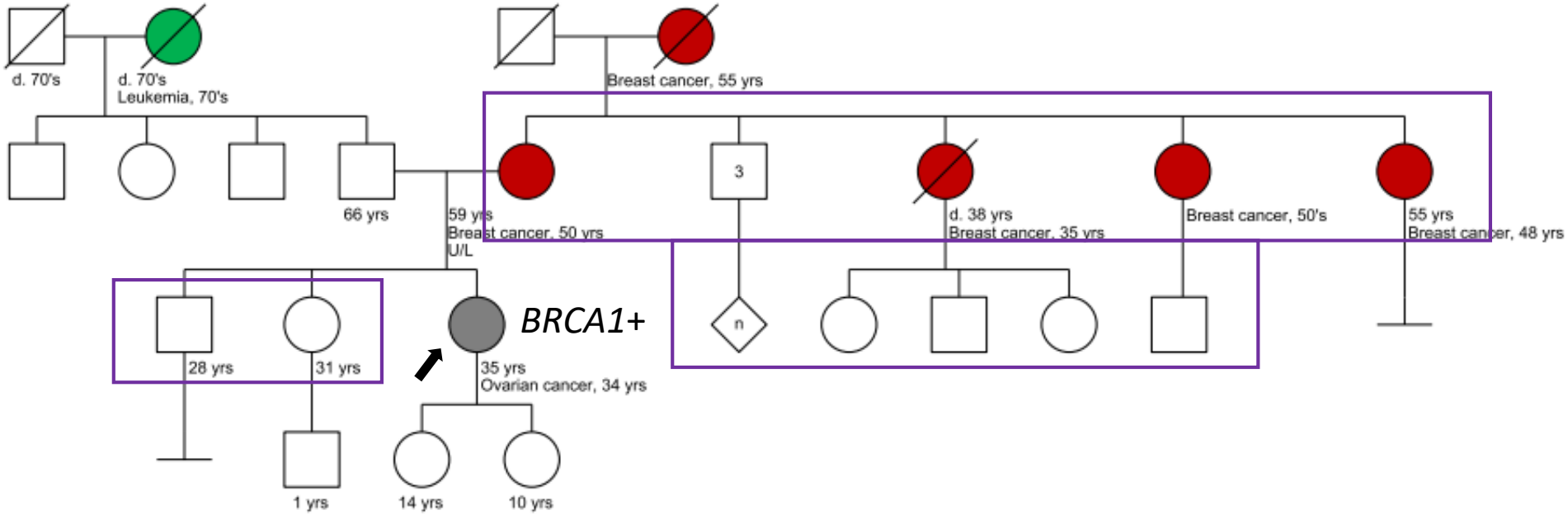

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Future of Genetics

- Patient-centered, personalized medicine
- Eligibility broadens over time
- Access increases with time

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Question & Answer