CANCER EDUCATION DAY

Genetic Markers:
Colorectal and Pancreatic Cancer

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November 12, 2021

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Presenter Disclosure

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  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** N/A
  - **Patents**: N/A
  - **Advisory Board:** N/A

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Objectives

- Review the main concepts of hereditary cancer
- Review hereditary syndromes relating to colorectal and pancreatic cancers
- *Colorectal and pancreatic cancers presenting in younger patients*
- Review the new 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

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

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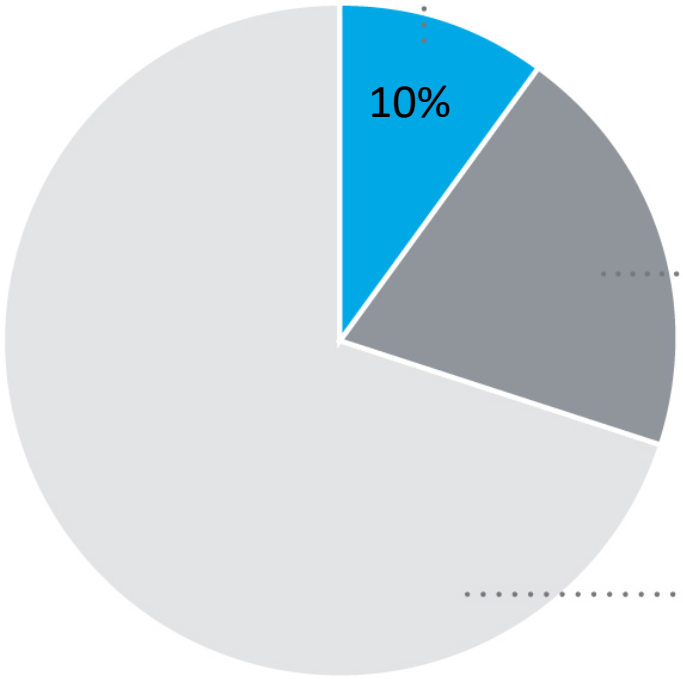
Concepts in Hereditary Cancer



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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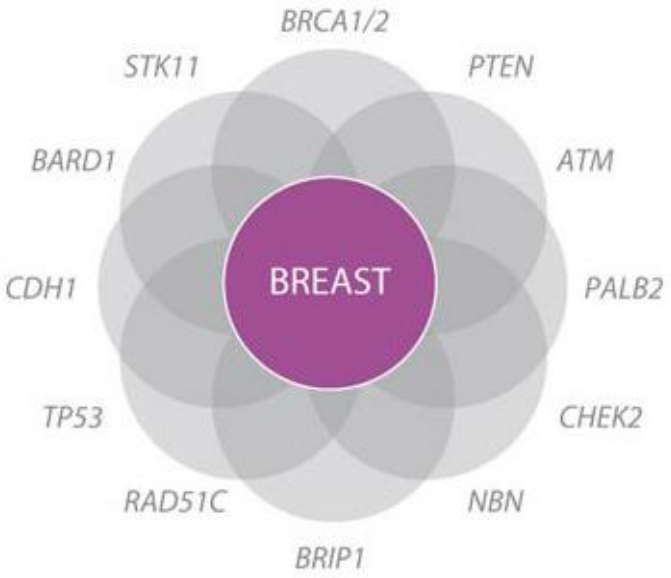
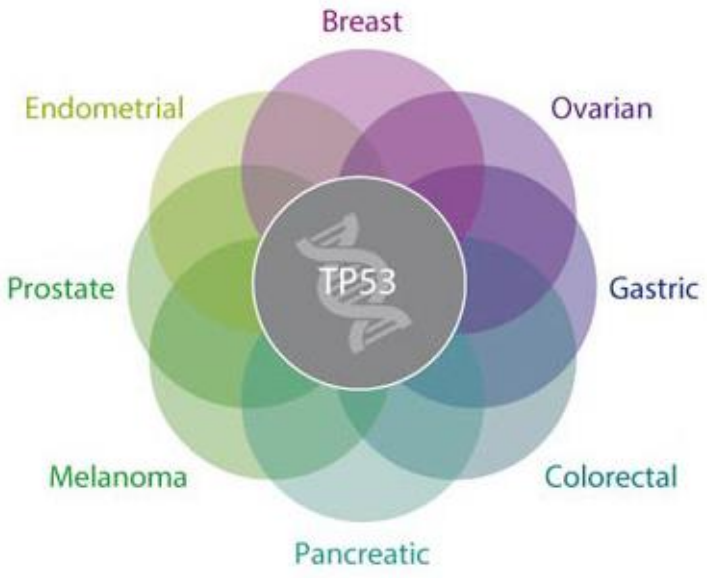
Concepts in Hereditary Cancer

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!

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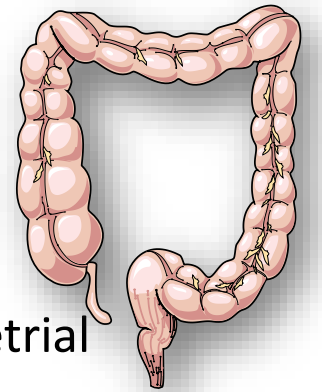
Lynch Syndrome



- Multiple cases in *close* relatives on same side of family:
  - colon
  - endometrial/uterine
  - ovary
  - small bowel
  - urothelial (transitional cell)
  - sebaceous neoplasm
  - keratocanthoma
  - *One must be diagnosed less than age 50.*

- Colon or uterine/endometrial cancer **less than or at 45**
- CRC <50, with one FDR/SDR with Lynch-related cancer less than or at 50
- Synchronous/metasynchronous colon or Lynch-related cancers (second primary <60)
- Abnormal MMR-IHC staining *(normal BRAF, normal MLH1 methylation)*

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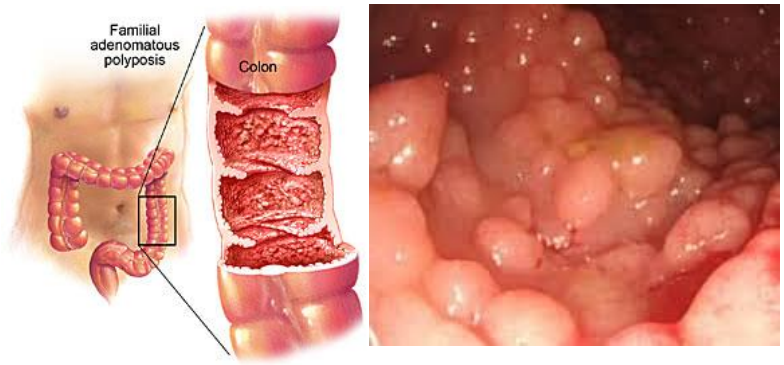
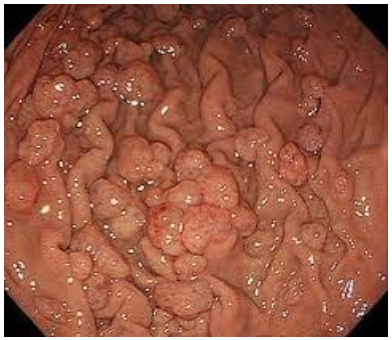
Hereditary Polyposis

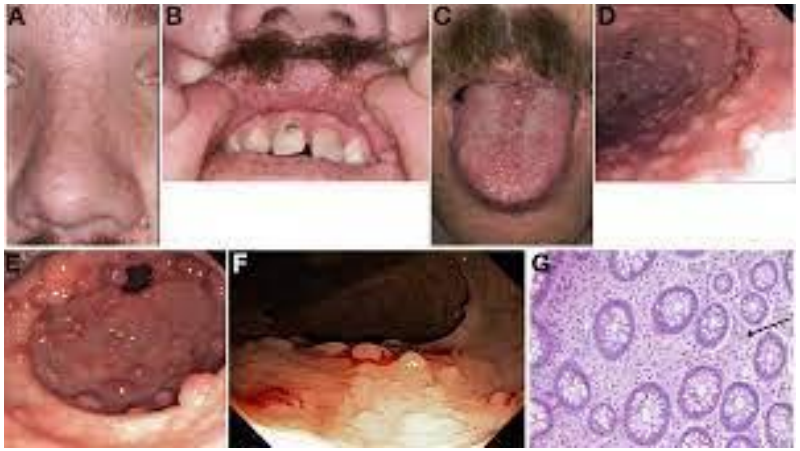
Tubular adenomas



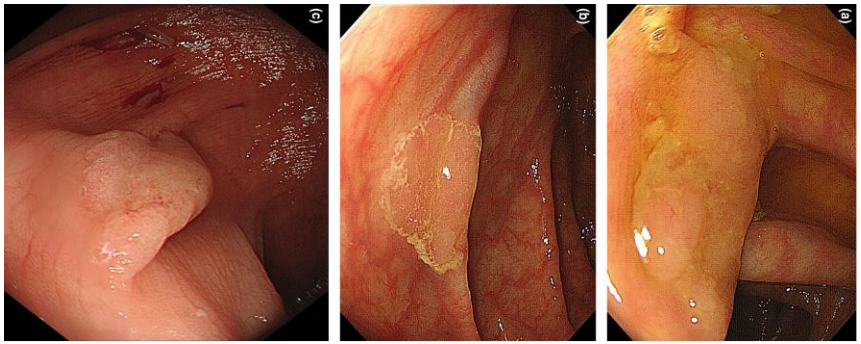
Fundic gland polyps



Hamartomatous polyps



Serrated (sessile) polyps



Polyposis Criteria

Table 1: Polyposis Table

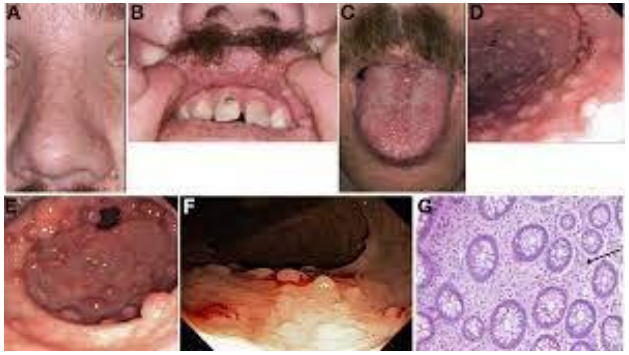
Number of polyps	Additional Risk Factors Required
≥20 colorectal adenomas	None
10-19 colorectal adenomas	≤60 years of age
5-9 colorectal adenomas	Personal history of 5-9 colorectal adenomas diagnosed at: • <40 years of age and extracolonic manifestation[18] commonly associated with FAP or MAP • <50 years of age and ≥1 of the following: CRC ≤50 years of age, EC ≤60 years of age, glioblastoma, astrocytoma, or ≥10 additional polyps (i.e., serrated adenoma, hyperplastic and especially unbiopsied polyps that could represent additional adenomas) Personal history of 5-9 colorectal adenomas with: • one FDR with of CRC <50, EC <60 or GBM or astrocytoma, OR • ≥2 FDR or SDR with CRC or EC at any age
Fundic gland polyposis (FPG)	• 100 or more FGP (may be described as carpeting) • Description of clustering, multiple FGP in absence of proton pump inhibitor (PPI) use and sparing the antrum and lesser curvature of the stomach • >30 FGP (in absence of PPI) sparing antrum and curvature + FDR who has path confirmed gastric cancer <50 or path confirmed FG polyposis
≥2 hamartomatous polyps	Clinical assessment for hamartomatous polyposis syndromes

Serrated Polyposis (RNF43 gene)

- Personal history of >=20 serrated polyps in colon/rectum, at least 5 being proximal to the rectum (think ***location***)
- Personal history of >=5 serrated polyps/lesions proximal to the rectum, all polyps >5mm and at least 2 polyps measuring 10mm (think ***size***)

Non-cancerous Findings of Interest

- Cowden syndrome (PTEN)

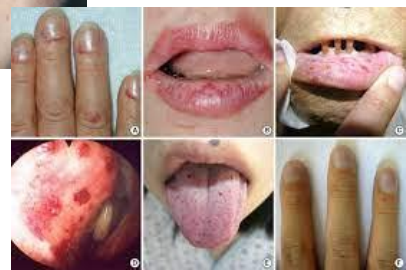


Feature	Percentage of patients affected
Mucocutaneous manifestations Trichilemmomas Papillomatous papules Acral keratosis	99%
Breast lesions Fibrocystic breast disease Adenocarcinoma	76% of affected females 30–50% of affected females
Macrocephaly	30–40%
Thyroid abnormalities Multinodular goiter Adenomas Thyroid carcinoma (usually follicular)	50–67% 3–10%
Gastrointestinal lesions Hamartomatous polyps Esophageal glycogenic acanthosis	30%
Genitourinary abnormalities Multiple uterine leiomyomas (fibroids) and/or bicornuate uterus	44% of affected females

Zbuk, Kevin & Eng, Charis. (2007). Hamartomatous polyposis syndromes. Nature clinical practice. Gastroenterology & hepatology. 4. 492-502. 10.1038/ncpgasthep0902.

- Puetz-Jeghers syndrome (*STK11*)
  - Mucocutaneous hyperpigmentation
  - Females: sex cord tumors w/ annular tubules (SCTAT), adenoma malignum of the cervix
  - Males: large calcifying Sertoli cell tumors of the testes
  - Cancers: Gastric, **pancreatic**, breast, ovarian, colon

- Juvenile Polyposis syndrome (BMPR1A, SMAD4)
  - “Juvenile" refers to the type of polyp, rather than to the age of onset
  - *SMAD4* = JPS & hereditary hemorrhagic telangiectasia (HHT) syndrome



“Other” genes

- *MSH3* – recessive polyposis
- *NTHL1* – Recessive CRC and mixed polyposis, possibly breast cancer and duodenal polyposis
  - Adenomatous, hyperplastic, serrated
- *GREM1* – Hereditary Mixed Polyposis Syndrome (HMPS) polyposis and CRC
  - Adenomatous, hyperplastic, serrated
- *POLE* & *POLD1* – CRC, adenomatous polyps, and endometrial cancer

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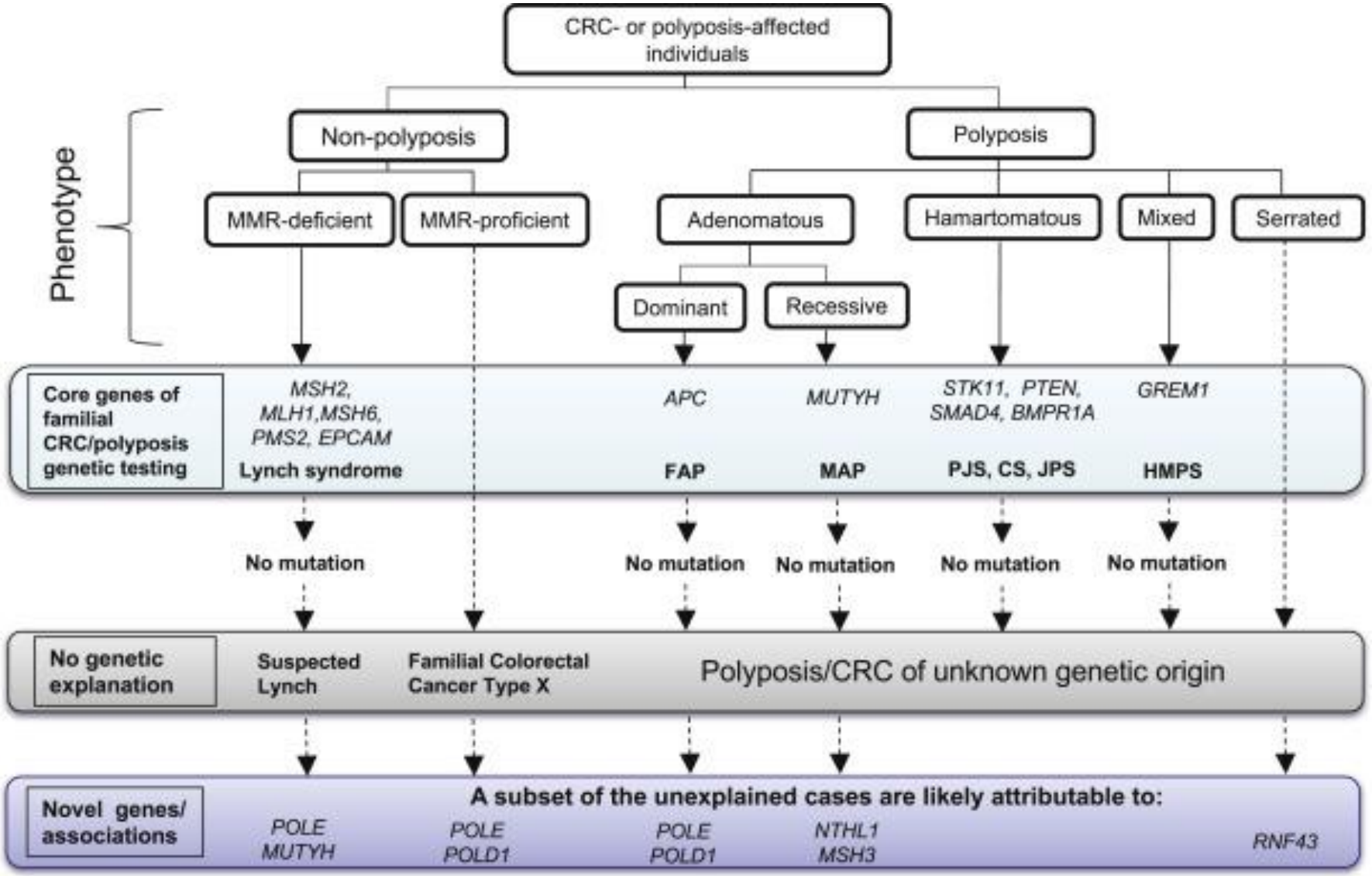

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Table 1 Well Established CRC and Polyposis Susceptibility Syndromes

Syndrome	Gene(s)	Inheritance	Pathway	Prevalence 1 in	Proportion of CRC	Mean Age of CRC Onset, Years	Polyp Burden	Predominant Lesion	Risk of CRC (95% CI if Provided)[a]	Extracolonic Malignancies
Hereditary CRC and Polyposis Syndromes										
Lynch	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Dominant	DNA Mismatch repair	1946[17] 2841[17] 758[17] 714[17] Unknown	3%-6%	43-45[14,18]	<5	Adenoma	F: 36% (25-61), M: 34% (25-50)[19] F: 37% (27-50), M: 47% (36-60)[19] F: 10% (5-17), M: 22% (14-32)[20] F: 11% (2.5-18), M: 19% (6-30)[21] F: 74% (56-92), M: 75% (63-87)[22]	Endometrial, ovarian, gastric, small bowel, urinary tract, brain, and pancreatic[23]
FAP/AFAP	*APC*	Dominant	Wnt signaling	10,000-31,250[24-26]	<1%	35-40[24,26]/54-62[27,28]	100-1000[27]/ 0-100[27]	Adenoma	100%[24]/69% (41-84)[29]	Thyroid carcinoma, CNS neoplasm, duodenal/ampullary adenomas[30]
MAP	*MUTYH*	Recessive	Base excision repair	Bi-allelic: 8073[17] Monoallelic: 45[17]	<1%	50-58[17,31]	0-100[32,33]	Adenoma	F: 72% (45-92), M: 75% (41-97)[34] F: 6% (4-9), M: 7% (5-11)[34]	Bladder, ovarian, and endometrial, gastric, breast, duodenal[35-39] Gastric, liver, breast, and endometrial[35]
JPS	*SMAD4, BMPR1A*	Dominant	TGF-β/BMP pathway	100,000[40]	<1%	42-44[41,42]	5-200[43]	Hamartoma	39%[41]	Upper GI cancer, stomach, and pancreatic[44]
PJS	*STK11*	Dominant	mTOR pathway	200,000[45]	<1%	34-46[46,47]	1-100[48]	Hamartoma	57%[49,b]	Breast, small bowel, gastric, esophageal, uterine, ovarian, pancreatic, lung, and testicular (Sertoli cell)[47,50]
CS	*PTEN*	Dominant	PI3K/AKT pathway	200,000-250,000[51]	<1%	44[52]	1-100[52]	Hamartoma	9%[53]	Thyroid, breast, kidney, and endometrial[54]
HMPS	*GREM1*	Dominant	TGF-β/BMP pathway	?	<1%	40[55]	1-15[56]	Mixed	?	?

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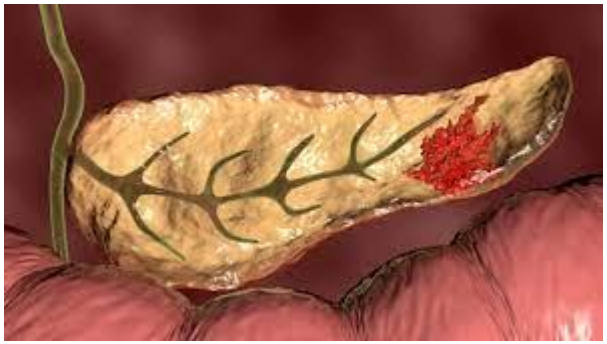
Hereditary Pancreatic cancer

- Testing criteria:
  - Personal history of pancreatic adenocarcinoma, any age



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Hereditary Pancreatic Cancer

Genes	Increased Risk	Other Cancers
ATM	Unclear	Breast
BRCA1	2- to 4-fold	Breast, ovary
BRCA2	3 to 8-fold	Breast, ovary, pancreas, larynx
CDKN2A	13- to 39-fold	Melanoma
Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*)	Up to 9- to 11-fold	Colon, endometrium, ovary, prostate?, etc.
PALB2	Unclear	Breast
STK11	132-fold	Breast, gastrointestinal, gynecologic

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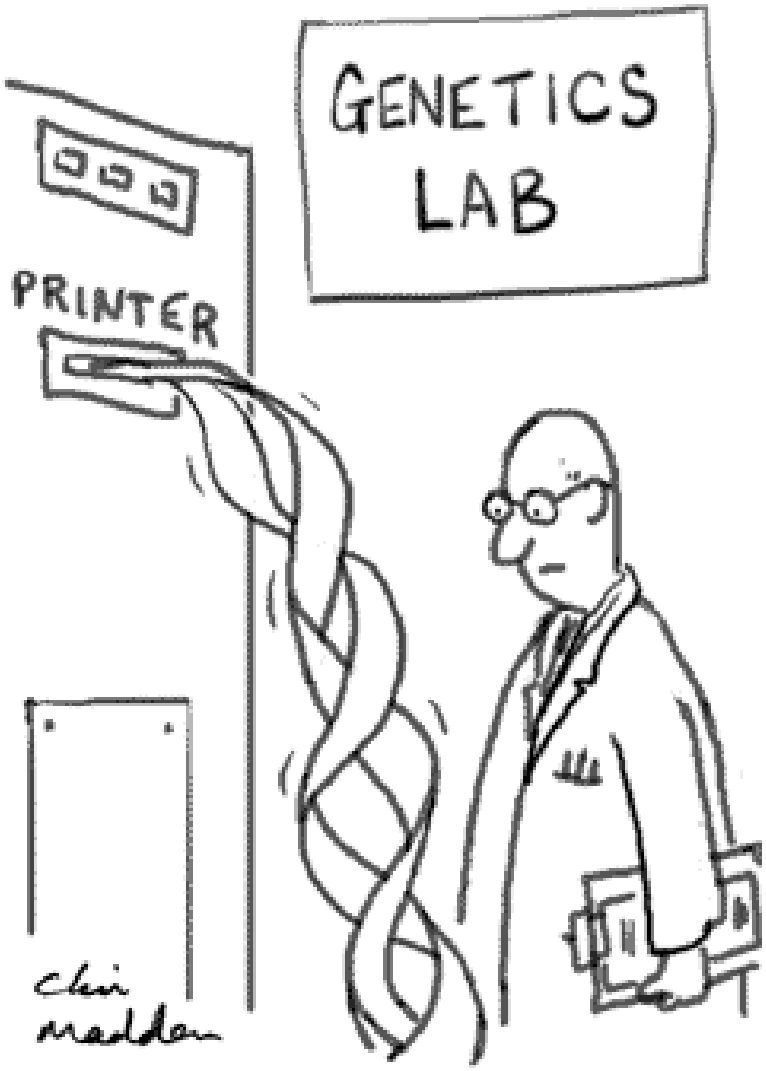
Genetic Testing



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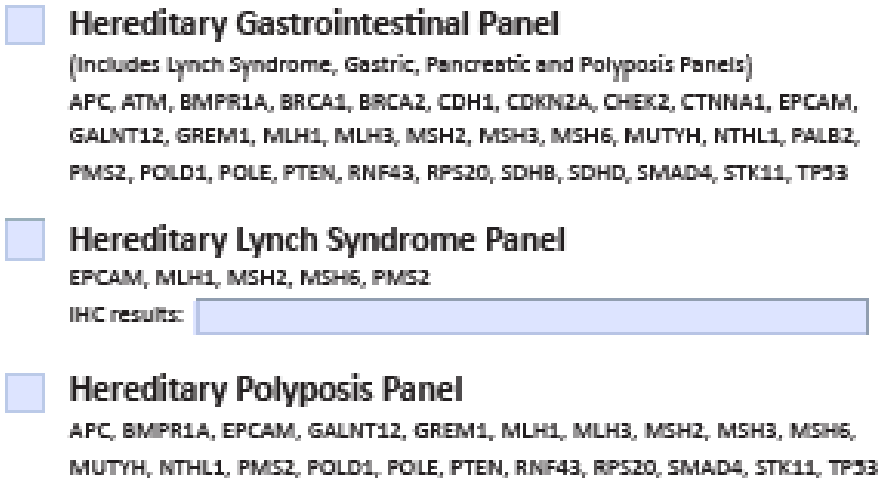
Genetic Testing: CRC/GI

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



☐ **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 Polyposis Panel**

APC, BMPR1A, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, SMAD4, STK11, TP53

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Genetic Testing: New in 2021!

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

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Genetic Testing: Gene 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 Polyposis Panel**
APC, BMPR1A, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, SMAD4, STK11, TP53

☐ **Hereditary Pancreatic Panel**
ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53

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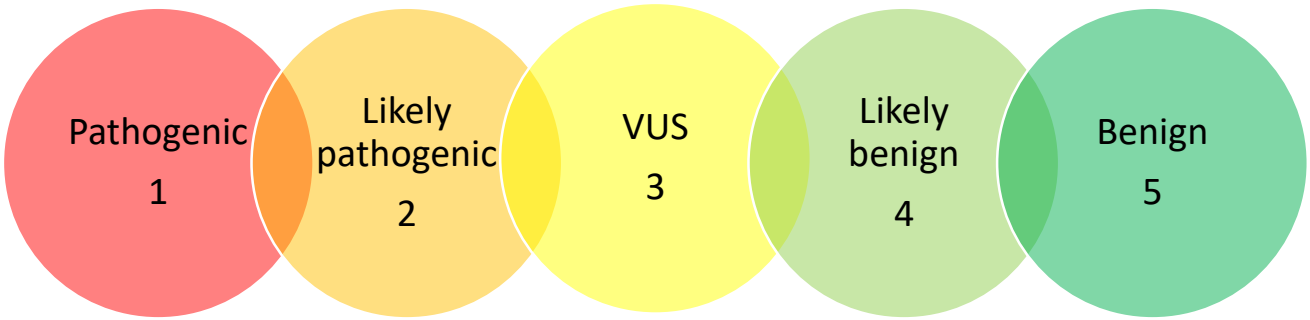
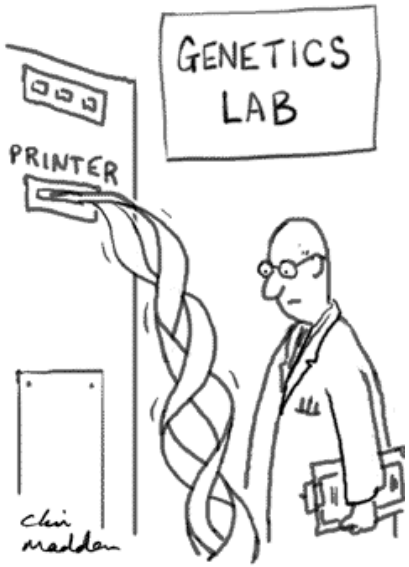
Genetic Testing: Results





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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

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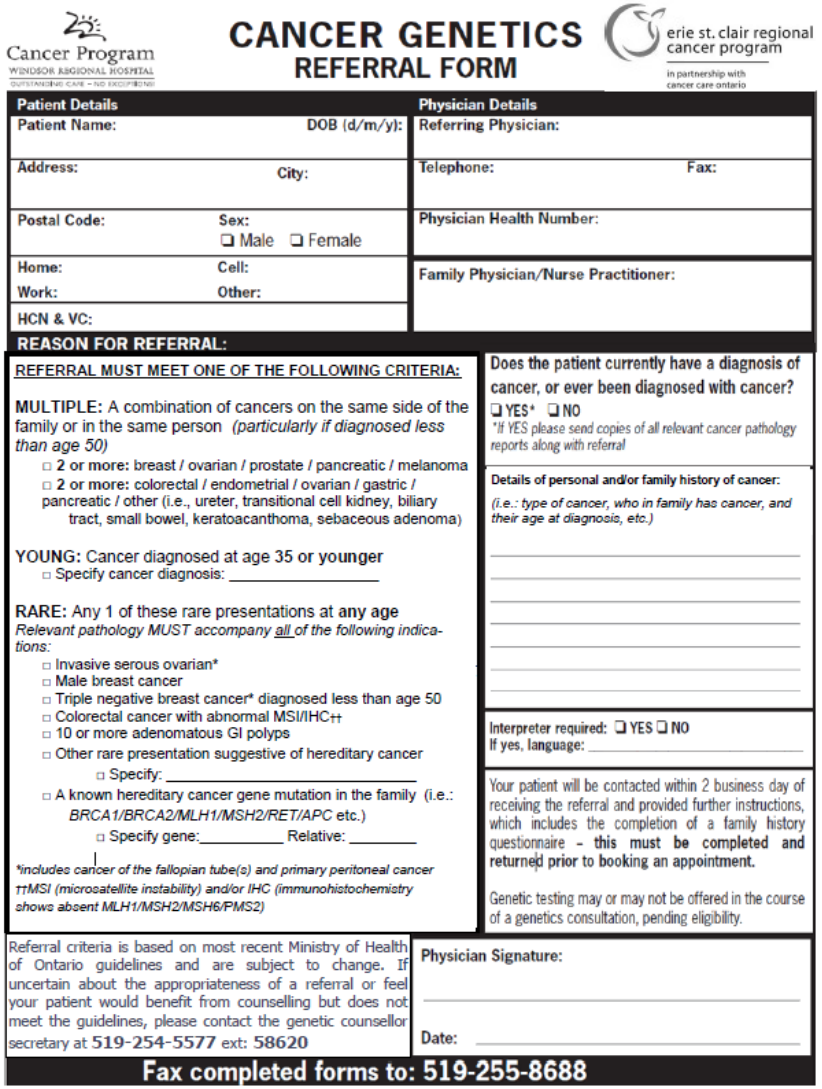
How to Refer

- Fax a referral form



Cancer Program
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CANCER GENETICS
REFERRAL FORM

erie st. clair regional cancer program
in partnership with cancer care ontario

Patient Details

Patient Name: DOB (d/m/y):

Address: City:

Postal Code: Sex: ❑ Male ❑ Female

Home: Cell:

Work: Other:

HCN & VC:

Physician Details

Referring Physician:

Telephone: Fax:

Physician Health Number:

Family Physician/Nurse Practitioner:

REASON FOR REFERRAL:

REFERRAL MUST MEET ONE OF THE FOLLOWING CRITERIA:

MULTIPLE: A combination of cancers on the same side of the family or in the same person *(particularly if diagnosed less than age 50)*

- ❑ **2 or more:** breast / ovarian / prostate / pancreatic / melanoma
- ❑ **2 or more:** colorectal / endometrial / ovarian / gastric / pancreatic / other (i.e., ureter, transitional cell kidney, biliary tract, small bowel, keratoacanthoma, sebaceous adenoma)

YOUNG: Cancer diagnosed at age 35 or younger

- ❑ Specify cancer diagnosis: _____

RARE: Any 1 of these rare presentations at **any age**

Relevant pathology MUST accompany all of the following indications:

- ❑ Invasive serous ovarian*
- ❑ Male breast cancer
- ❑ Triple negative breast cancer* diagnosed less than age 50
- ❑ Colorectal cancer with abnormal MSI/IHC††
- ❑ 10 or more adenomatous GI polyps
- ❑ Other rare presentation suggestive of hereditary cancer
  - ❑ Specify: _____
- ❑ A known hereditary cancer gene mutation in the family (i.e.: *BRCA1/BRCA2/MLH1/MSH2/RET/APC* etc.)
  - ❑ Specify gene:_____ Relative: _____

**includes cancer of the fallopian tube(s) and primary peritoneal cancer*
††MSI (microsatellite instability) and/or IHC (immunohistochemistry shows absent MLH1/MSH2/MSH6/PMS2)

Does the patient currently have a diagnosis of cancer, or ever been diagnosed with cancer?
❑ YES* ❑ NO
**If YES please send copies of all relevant cancer pathology reports along with referral*

Details of personal and/or family history of cancer:
(i.e.: type of cancer, who in family has cancer, and their age at diagnosis, etc.)

Interpreter required: ❑ YES ❑ NO
If yes, language: _____

Your patient will be contacted within 2 business day of receiving the referral and provided further instructions, which includes the completion of a family history questionnaire – **this must be completed and returned prior to booking an appointment.**

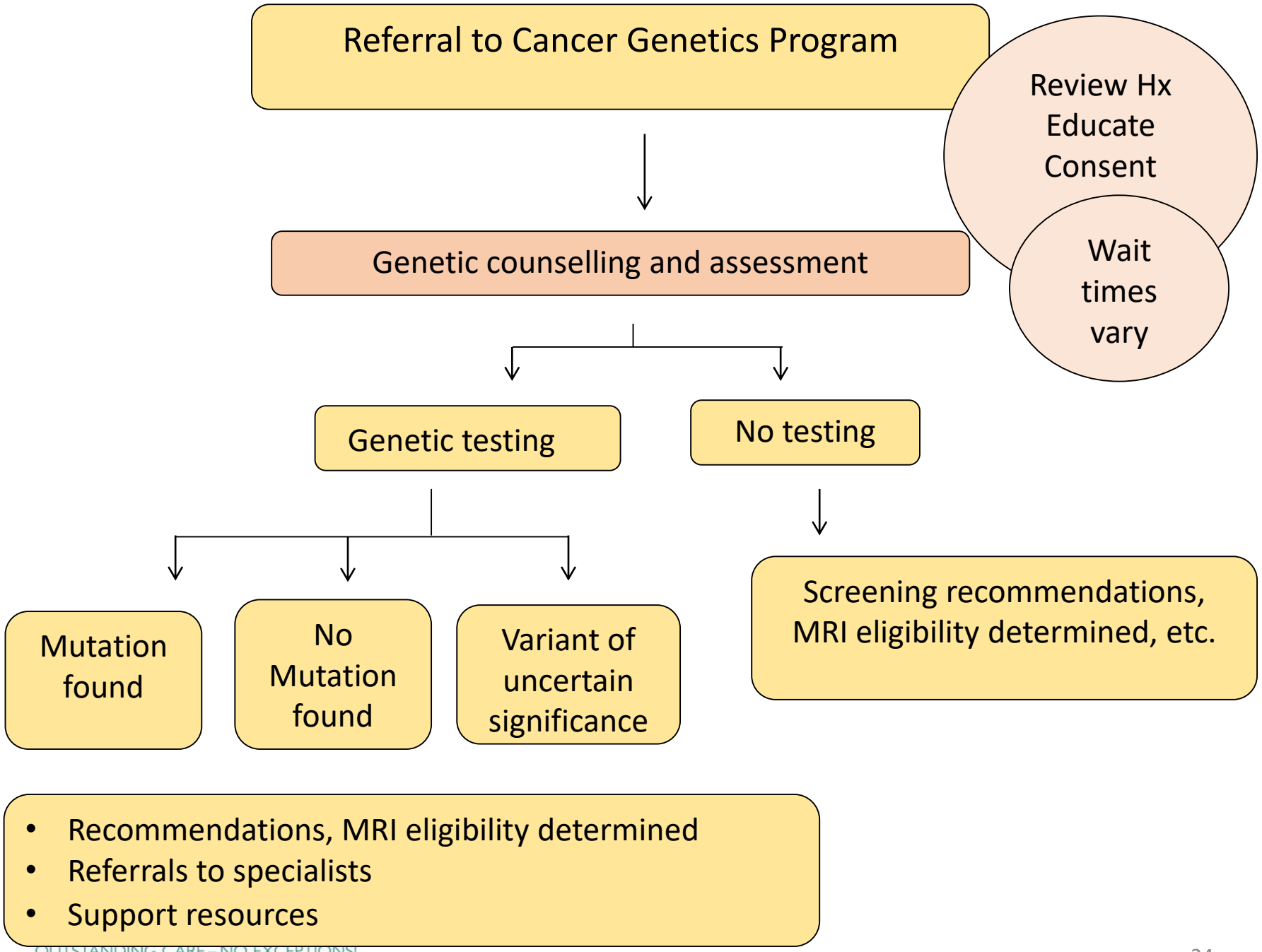
Genetic testing may or may not be offered in the course of a genetics consultation, pending eligibility.

Referral criteria is based on most recent Ministry of Health of Ontario guidelines and are subject to change. If uncertain about the appropriateness of a referral or feel your patient would benefit from counselling but does not meet the guidelines, please contact the genetic counsellor secretary at **519-254-5577** ext: **58620**

Physician Signature:

Date: _____

Fax completed forms to: 519-255-8688



- Recommendations, MRI eligibility determined
- Referrals to specialists
- Support resources

Post-test Counselling

- Information provided regarding:
  - Impacts on the family
  - Cancer surveillance recommendations
  - Risk reducing surgery
    - Further referrals to other specialties, as/if needed
  - Answer patient questions
- Cascade testing for the family

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Genetics is the future

- Genetic testing has become an integral part of patient care, and partnering with genetic counsellors has never been more important than now
- Clinical partnerships are critical
- Patient-centered, personalized medicine

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Question & Answer

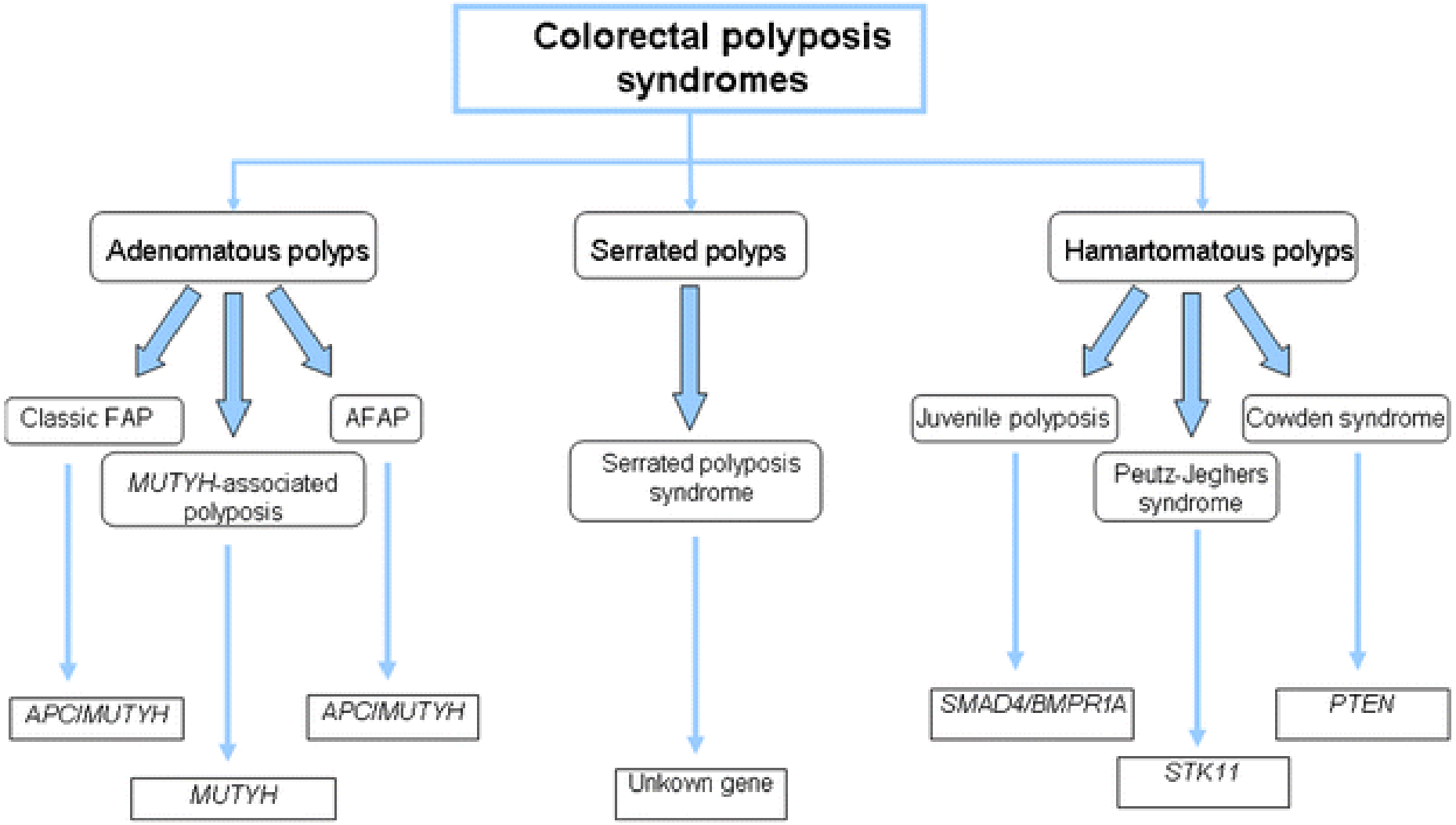
Colorectal polyposis syndromes
Adenomatous polyps
Serrated polyps
Hamartomatous polyps
Classic FAP
AFAP
MUTYH-associated polyposis
Serrated polyposis syndrome
Juvenile polyposis
Peutz-Jeghers syndrome
Cowden syndrome
APC/MUTYH
APC/MUTYH
MUTYH
Unkown gene
SMAD4/BMPR1A
STK11
PTEN

TABLE 2. **Hereditary/Familial Syndromes Associated With Pancreatic Ductal Adenocarcinoma**

Syndrome	Identified genes	Clinical presentation	Cumulative risk of PDAC	Relative risk of PDAC
Peutz-Jeghers syndrome	*STK11/LKB1*	Gastrointestinal hamartomatous polyps; mucocutaneous pigmentation; high-risk gastrointestinal, breast, ovarian, endometrial, and lung cancers	Up to 36% lifetime risk	132-fold
Familial pancreatitis syndrome	*PRSS1, SPINK1, PRSS2, CFTR*	Recurring acute pancreatitis and chronic pancreatitis	Up to 53% at age 75 years	26- to 87-fold
Familial malignant melanoma syndrome	*P16/CDKN2A*	Multiple atypical nevi and history of melanoma and other tumors such as breast, lung, endometrium	Up to 17% at age 75 years	13- to 46.6-fold
Lynch syndrome	Colorectal, endometrial, stomach, small intestine, urinary tract, brain cancers	*MLH1, MSH2, MSH6, PMS2*	3.7% at age 70 years	8.6-fold
Hereditary breast–ovarian cancer syndrome	*BRCA1, BRCA2, PALB2*	Breast and ovarian cancer	1.5%-4.0% at age 70 years; more in *BRCA2*	*BRCA1*: 4- to 6-fold *BRCA2*: 3- to 22-fold *PALB2*: 6-fold
Familial pancreatic cancer	2 or more first-degree relatives with PDAC	Unknown in most families	3 or more first-degree relatives with PDAC: up to 16%-40% 2 first-degree relatives with PDAC: up to 12%	3 or more first-degree relatives with PDAC: 32-fold 2 first-degree relatives with PDAC: 6-fold 1 first-degree relative with PDAC: 2- to 5-fold

PDAC; pancreatic ductal adenocarcinoma

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