Fred Hutch Cancer Center

Hereditary Cancer Syndromes

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Credit to Marshall Horowitz for several slides

UW Medicine

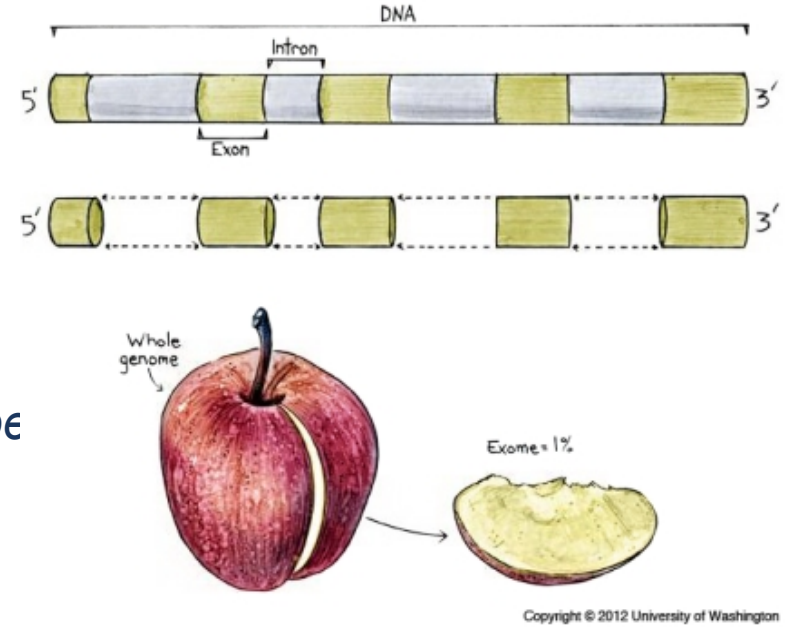
Genetics 101

Whole genome: 3.2 billion base pairs

Only 1% of this codes for genes (exome)

Exome comprises ~20,000 genes

Only 4,876 of these are associated with a human phenotype

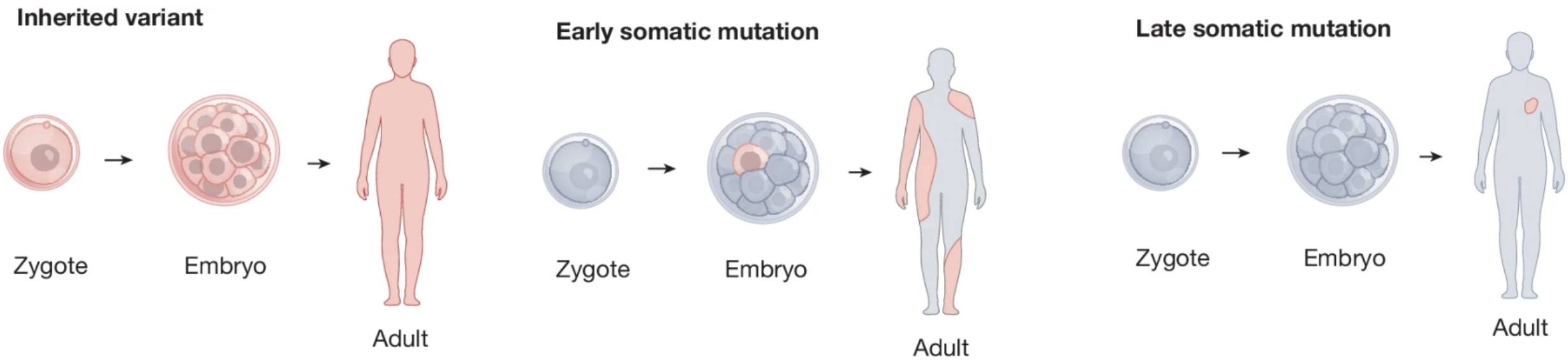


Germline variants (Any two humans differ at ~4 million bases)

Germline genetic variants *are present at fertilization*

Different variants often referred to as ***alleles***

Germline vs. post-zygotic vs. somatic variant



These are associated with hereditary cancer syndromes

Nomenclature for germline genetic variants

Distinction between common and rare variants

Common variants (Allele Frequency>0.5%):

Most benign, and some are associated with increased risk of diseases (*i.e.,* "GWAS variants")

Rare variants (Allele Frequency <0.5%):

Most benign

Some associated with **Mendelian disorders**

Classification of rare genetic variants*:

Pathogenic Variant: Sufficient evidence to classify as capable of causing disease.

Likely Pathogenic Variant: Strong evidence in favor of pathogenicity.

Variant of Uncertain Significance (VUS): Limited and/or conflicting evidence regarding pathogenicity.

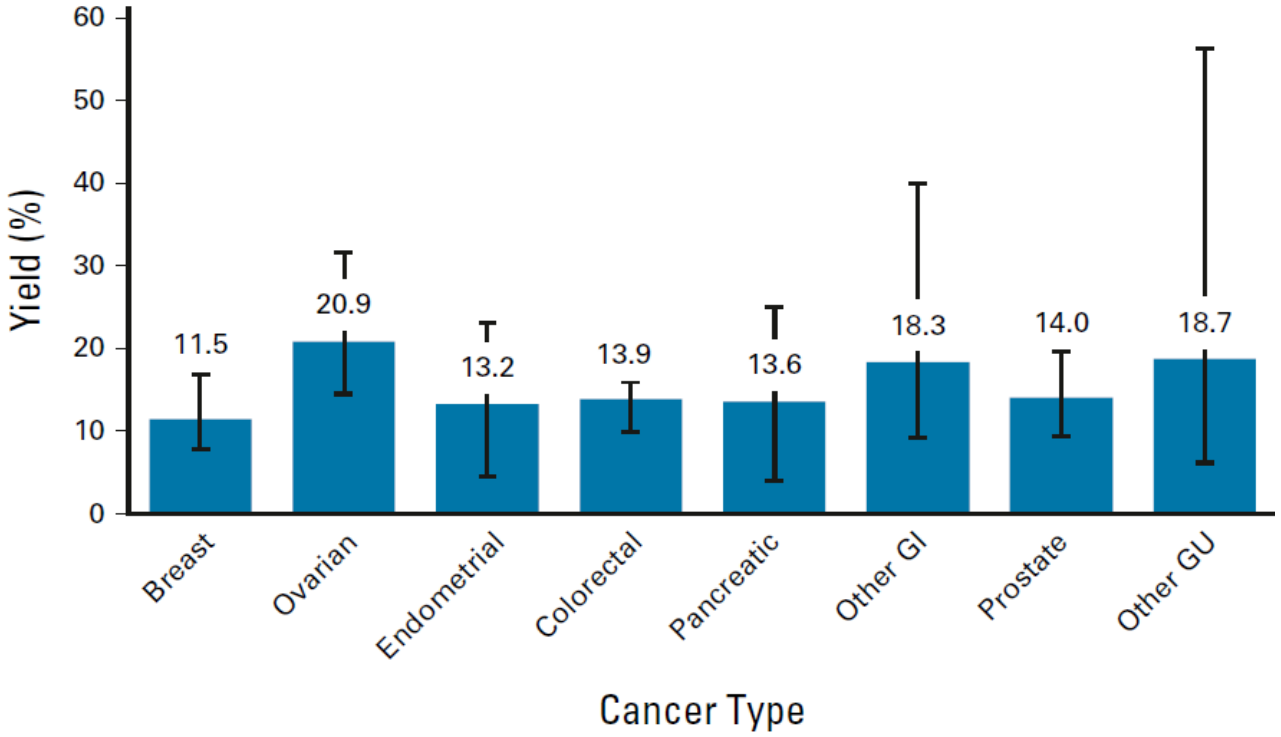
Likely Benign Variant: Strong evidence against pathogenicity.

Benign: Very strong evidence against pathogenicity.

*__ACMG v3 guidelines:__ Richards et al *Genetics Medicine* 2015

Diagnostic yield of germline P/LP variants in individuals with cancer

Individuals with common solid tumors unselected for family history or other putative risk factors



Esplin et al., JCO Precision Oncology (2022)

Genetic testing strategy

Indication-driven testing: Individuals with suspected genetic conditions who undergo clinical genetic testing

Genomic screening: Individuals without a suspected genetic condition who undergo genetic testing

> ***Assumption underlying genomic screening:*** There are genetic conditions wherein prior knowledge of that condition would enable precision genomic medicine

Clinical genomic medicine currently is grounded in indication-driven testing. Genomic screening is an emerging research topic, and may in the future be implemented clinically

Outline of talk

Li-Fraumeni Syndrome

Hereditary Breast and Ovarian Cancers

Lynch Syndrome

Familial Adenomatous Polyposis

Multiple Endocrine Neoplasia and Familial Medullary Thyroid Cancer Syndromes

Li-Fraumeni Syndrome (LFS)

Inheritance: Autosomal Dominant (AD)

Gene: *TP53*

Mechanism: Loss-of-function (LOF)

Prevalence: 1:3,000 to 1:10,000

Cancer risk:
Breast cancer: >60% (often young)
Pancreatic cancer: 5%
Prostate cancer: 25-50%
Sarcomas: 15-22%
CNS tumor: 6-19%
Adrenocortical carcinoma
GI cancers
ALL
Others

Li-Fraumeni Syndrome (LFS) - Testing

Indications for genetic testing (NCCN guidelines):

Classic LFS Criteria (must meet all three):

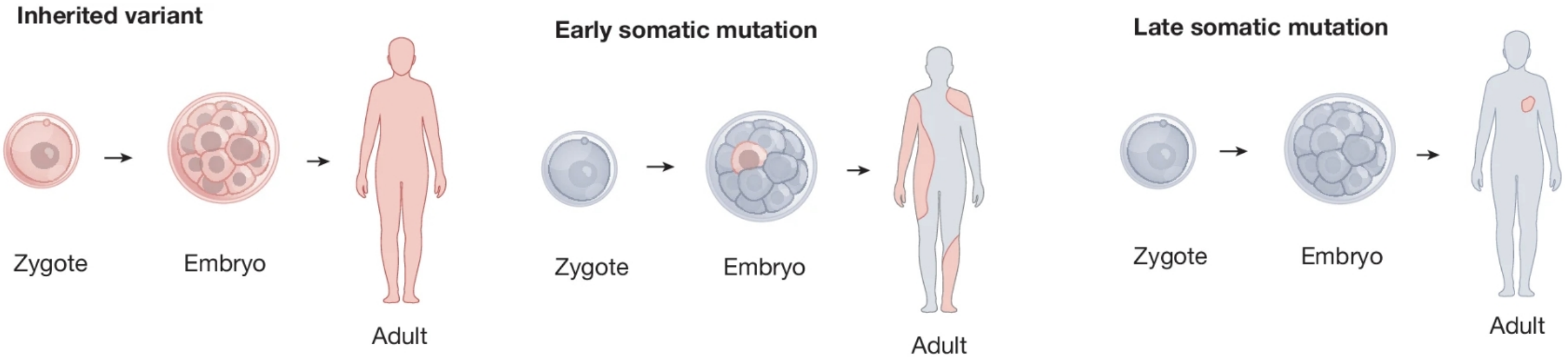
1. Sarcoma at age <45
2. First degree relative with a cancer at age <45
3. First- or second-degree relative with a cancer at age <45 or sarcoma at any age

Chompret Criteria (any of the below):

1. Tumor from LFS spectrum at age <46 AND First- or second-degree relative with a LFS spectrum tumor at age <56 (with exception of breast cancer if proband also has breast cancer)
2. Two or more LFS spectrum tumors at age <46 (with exception of multiple breast cancer)
3. ACC, choroid plexus carcinoma, or embryonal anaplastic rhabdomyosarcoma at any age
4. Breast cancer at age <31

Pediatric hypodiploid ALL or family history of pediatric hypodiploid ALL

Li-Fraumeni Syndrome (LFS) - Testing



These are considered LFS

If isolated in blood only, this is likely clonal hematopoiesis of indeterminate potential (CHIP)

Mosaic variants identified in the blood should be followed up using testing from another site (*i.e.*, skin fibroblasts) to distinguish if variant is CHIP or LFS

Li-Fraumeni Syndrome (LFS) - Management

Breast cancer:

- Annual Breast MRI age 20-29
- Annual Breast MRI AND mammogram age 30-75
- Consider risk reduction surgery

Other cancers:

- Annual whole-body MRI (including brain)
- Annual PSA age 40+
- Colonoscopy and upper endoscopy every 2-5y age 25+ of 5yr prior to earliest known colorectal or gastric cancer in family
- Annual dermatology exam
- Pancreatic cancer screening if family history of pancreatic cancer in 1st or 2nd degree relative

Hereditary Breast and Ovarian Cancer Syndrome

Inheritance: Autosomal Dominant (AD)

Genes: *BRCA1, BRCA2, PALB2, others*

Mechanism: Loss-of-function (LOF)

Prevalence: 1:100-200

Cancer risk:

	BRCA1	***BRCA2***	***PALB2***
Breast cancer	F: 60-72% risk M: 0.2-1.2% risk	F: 55-69% risk M: 1.8-7.1% risk	F: 32-53% risk
Ovarian cancer	39-58% risk	13-29% risk	5% risk
Pancreatic cancer	<5% risk	5-10% risk	5-10% risk
Prostate cancer	7-26% risk	19-61% risk	Aggressive/metastatic dz.
Other cancers		Melanoma	

Hereditary Breast and Ovarian Cancer Syndrome - Testing

Indications for genetic testing (NCCN guidelines):

Has breast cancer at age <=50 (and one of the below)

- Genetic testing would impact treatment decisions
- Triple-negative breast cancer
- Multiple primary breast cancers
- Lobular breast cancer AND personal or family history of diffuse gastric cancer
- Male breast cancer
- Ashkenazi Jewish ancestry
- Family history of 1st, 2nd, or 3rd degree relative with:
  - Breast cancer at age <=50, OR Male breast cancer, OR Ovarian cancer, OR Pancreatic cancer, OR Prostate cancer (metastatic or high/very-high group)
  - >=2 additional relatives on same site with breast and/or prostate cancer
- >5% probability of genetic diagnosis on Tyer-Cuzick, BRCAPro, or CanRisk model

No breast cancer, but 1st or 2nd degree relative who meets one the above criteria
No breast cancer, but >5% probability of genetic diagnosis on above models

Hereditary Breast and Ovarian Cancer Syndrome - Testing

Indications for genetic testing (NCCN guidelines):

Has epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) (any age)

Has non-epithelial ovarian cancer (any age)

No ovarian cancer, but (one of the below)

- Family history of 1st, or 2nd, degree relative with epithelial ovarian cancer
- >5% probability of genetic diagnosis on Tyer-Cuzick, BRCAPro, or CanRisk model

Hereditary Breast and Ovarian Cancer Syndrome - Testing

Indications for genetic testing (NCCN guidelines):

Has prostate cancer (and one of the below)

- Metastatic or node-positive prostate cancer
- Very high-risk or high-risk disease
- Ashkenazi Jewish ancestry
- Family history of 1st, 2nd, or 3rd degree relative with:
  - Breast cancer at age <=50
  - Male breast cancer
  - Ovarian cancer
  - Pancreatic cancer
  - Prostate cancer (metastatic or high/very-high group)
  - >=2 additional relatives on same site with breast and/or prostate cancer

No prostate cancer, but 1st or 2nd degree relative who meets one the above criteria

Hereditary Breast and Ovarian Cancer Syndrome - Testing

Indications for genetic testing (NCCN guidelines):

Has exocrine pancreatic cancer (and one of the below)

Neuroendocrine pancreatic tumor

No pancreatic cancer, but 1st degree relative with exocrine pancreatic cancer

Hereditary Breast and Ovarian Cancer Syndrome - Management

Breast cancer:

- Annual Breast MRI age 25-29
- Annual Breast MRI AND mammogram age 30-75
- Consider risk reduction surgery
- In men with *BRCA2* P/LP variants consider annual mammogram at age 50 or 10 years prior to earliest known male breast cancer in family

Pancreatic cancer:

- Consider pancreatic cancer (PC) screening (annual MRI/MRCP and/or EUS) for individuals with PC in ≥1 1st or 2nd degree relative presumed to have same variant

Other cancers:

- Consideration for salpingectomy with delayed oophorectomy, BSO (stronger recommendation for individuals with *BRCA1* P/LP variants)
- Consideration of OCPs or levonorgestrel IUD for ovulation suppression

Use of PARP1 inhibitors for management

Lynch Syndrome vs Familial Adenomatous Polyposis (FAP)

Feature	Lynch Syndrome	FAP (*APC*)	Attenuated FAP (*APC*)	MAP (*MUTYH*)
# Polyps	0-50 usually	>100	10-99	5 to >700
Inheritance	autosomal dominant	autosomal dominant	autosomal dominant	autosomal recessive
Cancer(s)	colon, endometrial, gastric, ovarian	colon, small bowel, other	colon, small bowel	colon
Median onset age (years)	44-61 cancer	39 cancer (16 polyps)	50-55 cancer	47 cancer
DNA repair phenotype	MSI+ (microsatellite instability)	CIN+ (chromosomal instability – not clinically testable)	-	MSI-

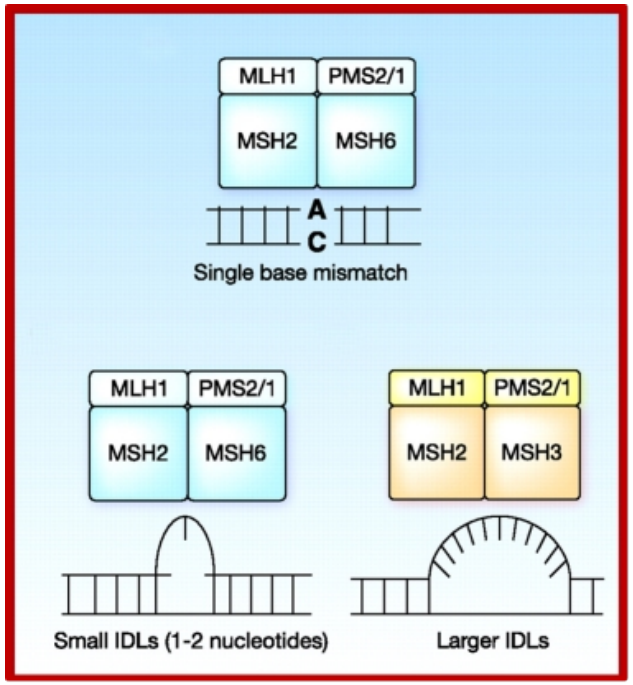
Lynch Syndrome

Inheritance: Autosomal Dominant (AD)

Gene: *MLH1, MSH2, MSH6, PMS2, EPCAM*

Mechanism: Loss-of-function (LOF)

Prevalence: 1:279 (*MLH1* 1:1,946; *MSH2* 1:2,841; *MSH6* 1:758; *PMS2* 1:714, *EPCAM* rare)



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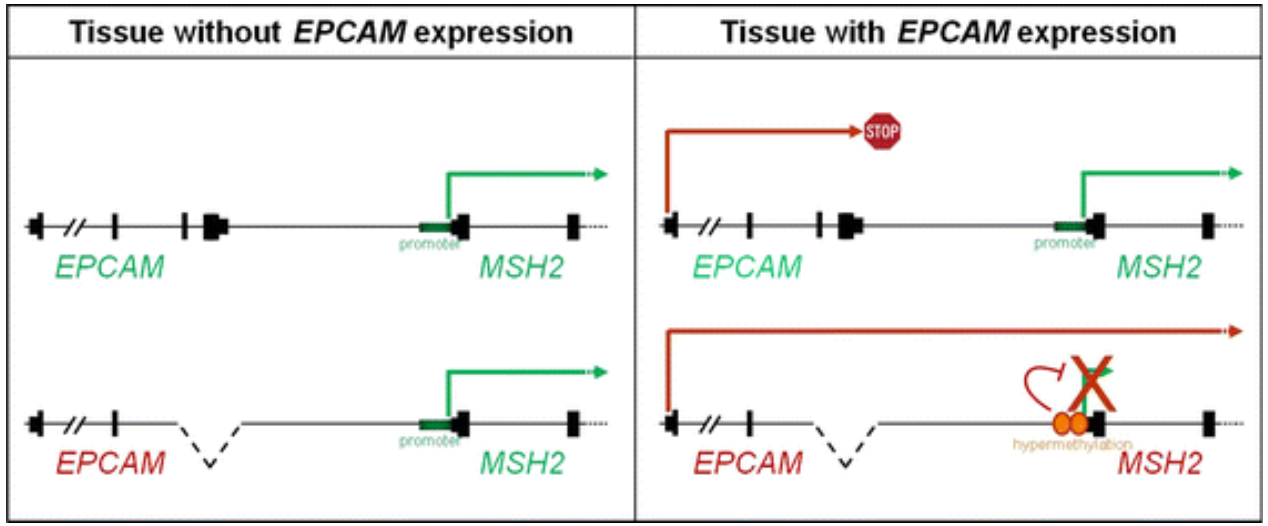


Deletions of a transcriptional stop signal in an upstream gene (*EPCAM*) leads to hypermethylation and loss of expression of *MSH2*

Martin et al. 2010 Cancer Research

Lynch Syndrome

Cancer risk:

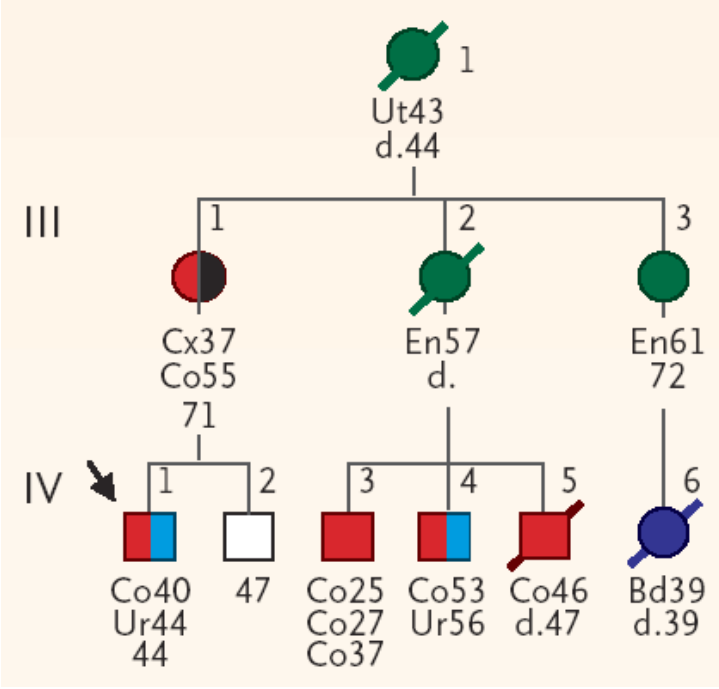
	MLH1	*MSH2/EPCAM*	*MSH6*	*PMS2*
Colorectal	46-61%	33-52%	10-44%	8.7-20%
Endometrial	34-54%	21-57%	16-49%	13-26%
Ovarian	4-20%	8-38%	1-13%	<3%
Renal pelvis/ureter	0.2-5%	2.2-28%	0.7-5.5%	
Bladder	2-7%	4.4-12.8%	1-8.2%	
Gastric	5-7%	0.2-9.0%	1-7.9%	
Small bowel	0.4-11%	1.1-10%	1-4%	
Pancreas	6.2%	0.5-1.6%	1.4-1.6%	
Biliary tract	1.9-3.7%	0.02-1.7%	0.2-1%	
Prostate	4.4-13.8%	3.9-23.8%	2.5-11.6%	
Brain	0.7-1.7%	2.5-7.7%	0.8-1.8%	
Other	Breast (female), skin	Breast (female), skin, sarcoma	Breast (female), skin	

Variable Expressivity and Lynch Syndrome

Cancer Sites

- Colon or rectum
- Bile duct
- Endometrium or uterus
- Pancreas
- Ureter
- Ovary
- Brain tumor
- Non-HNPCC cancer

Csu	Cancer site undetermined
Cx	Cervix
Eso	Esophagus
Mmel	Malignant melanoma
Pro	Prostate
Tes	Testicle



Lynch & de la Chapelle, 2003

Lynch Syndrome (LS) – Genetic Testing

Indications for genetic testing (NCCN guidelines):

Has LS-related cancer (and one of the below)

- MMR deficiency on tumor testing
- Diagnosed at age <50
- More than one LS-related cancer
- Family history of 1st, or 2nd degree relative with LS-related cancer diagnosed at age <50
- Family history of two or more 1st or 2nd degree relative with LS-related cancer diagnosed at any age

No LS-related cancer, but (one or below):

- 1st degree relative with colorectal or endometrial cancer diagnosed at age <50
- 1st or 2nd degree relative with colorectal or endometrial cancer AND another LS-related cancer diagnosed at any age
- Two or more 1st or 2nd degree relatives with LS-related cancer, with one diagnosed at age <50
- Three or more 1st or 2nd degree relatives with LS-related cancer diagnosed at any age

>=5% probability of genetic diagnosis using validated model

Lynch Syndrome (LS) – Genetic Testing

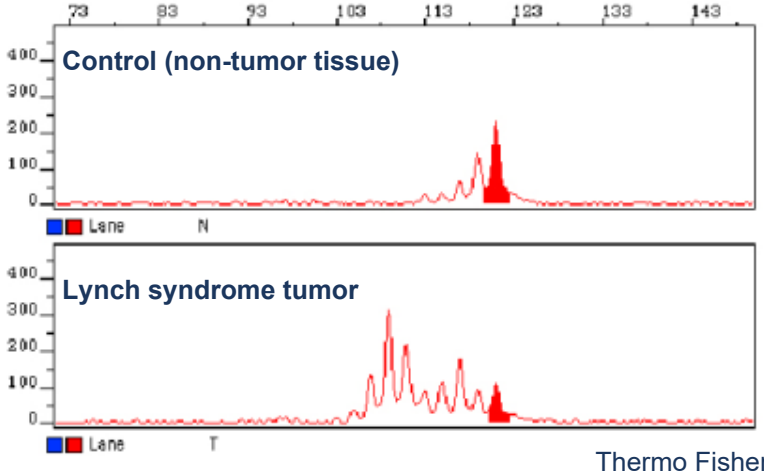
Amsterdam criteria: *"3-2-1 rule" (3 affected members, 2 generations, 1 under age 50)*

No LS-related cancer, but (one or below):

- 1st degree relative with colorectal or endometrial cancer diagnosed at age <50
- 1st or 2nd degree relative with colorectal or endometrial cancer AND another LS-related cancer diagnosed at any age
- Two or more 1st or 2nd degree relatives with LS-related cancer, with one diagnosed at age <50
- Three or more 1st or 2nd degree relatives with LS-related cancer diagnosed at any age

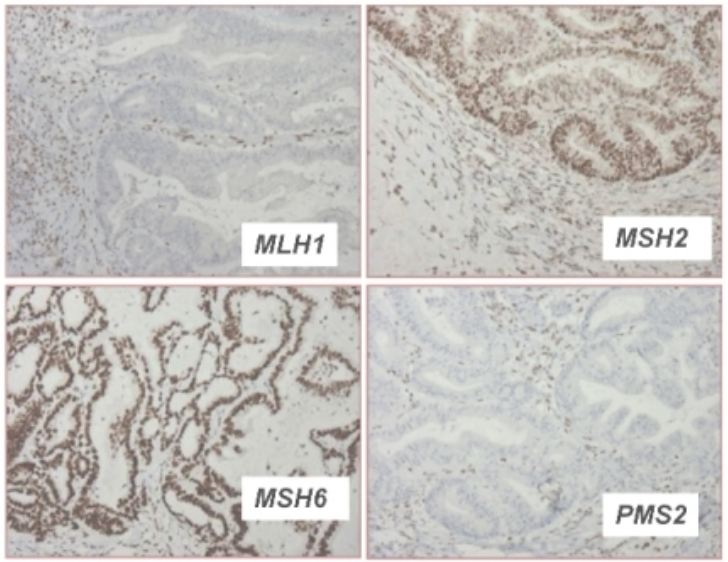
Lynch Syndrome – Tumor Testing

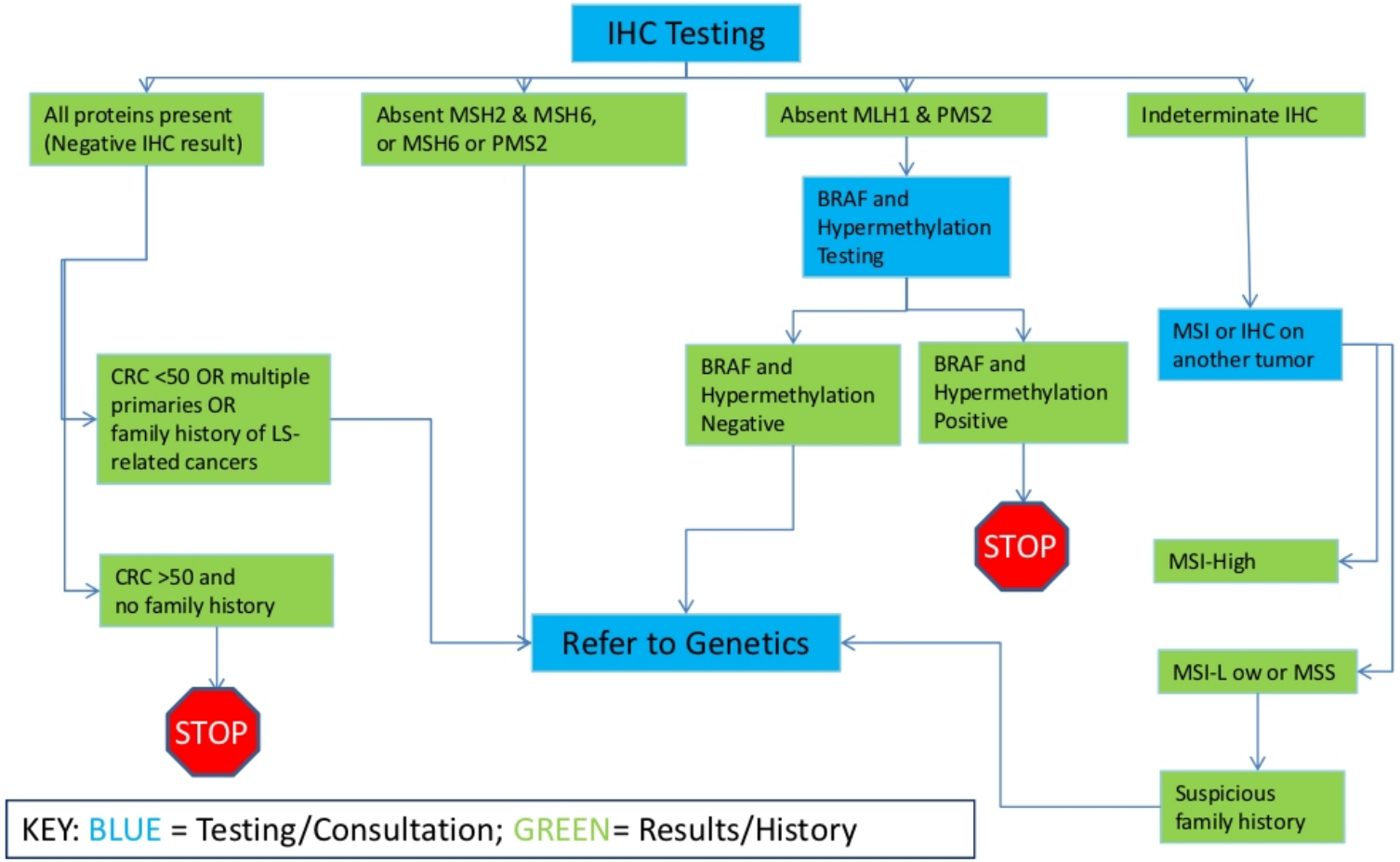
Microsatellite instability (MSI)



Thermo Fisher

Immunohistochemistry (IHC)





Lynch Syndrome – Management

Colorectal cancer:

- Colonoscopy every 1-2 years starting age 20-25 or 2-5y prior to earliest CRC in family
- Consider daily aspirin
- Consider modifications for *PMS2*-associated LS

Endometrial cancer:

- Patient education regarding EC symptoms

Ovarian cancer:

- Consider BSO

Gastric and small bowel cancer:

- EGD every 2-4y starting at age 30-40
- Testing and treatment of *H. pylori*

Lynch Syndrome – Management

Pancreatic cancer:

- Consider pancreatic cancer (PC) screening (annual MRI/MRCP and/or EUS) for individuals with PC in ≥1 1st or 2nd degree relative presumed to have same variant

Skin cancer:

- Consider skin exam every 1-2 years

Immunotherapies have shown promise for treating cancer in individuals with Lynch syndrome

Familial Adenomatous Polyposis (FAP)

Inheritance: Autosomal Dominant (AD)

Gene: *APC*

Mechanism: Loss-of-function (LOF)

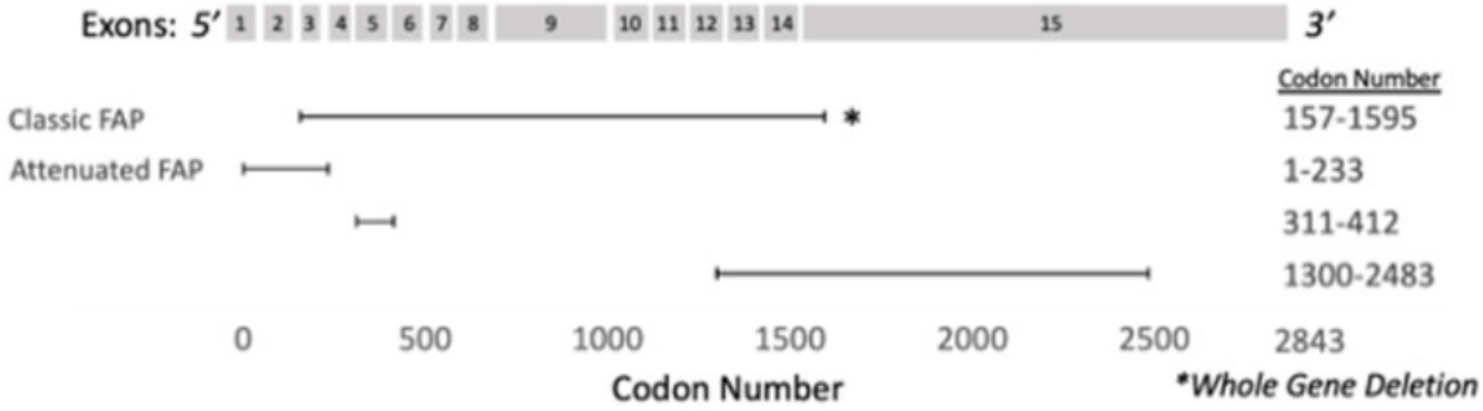
Prevalence: 1:6,850 to 1:31,250

Cancer risk:

	Classic FAP	Attenuated FAP	Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)
Colorectal	100% risk	70% risk	Rare
Duodenal	<1-10% risk		
Gastric	0.1-7.1% risk	0.1-7.1% risk	12-25%
Desmoid tumors	10-24% risk		
Thyroid (papillary)	1.2-12% risk		
Hepatoblastoma	0.4-2.5% risk		

Familial Adenomatous Polyposis (FAP)

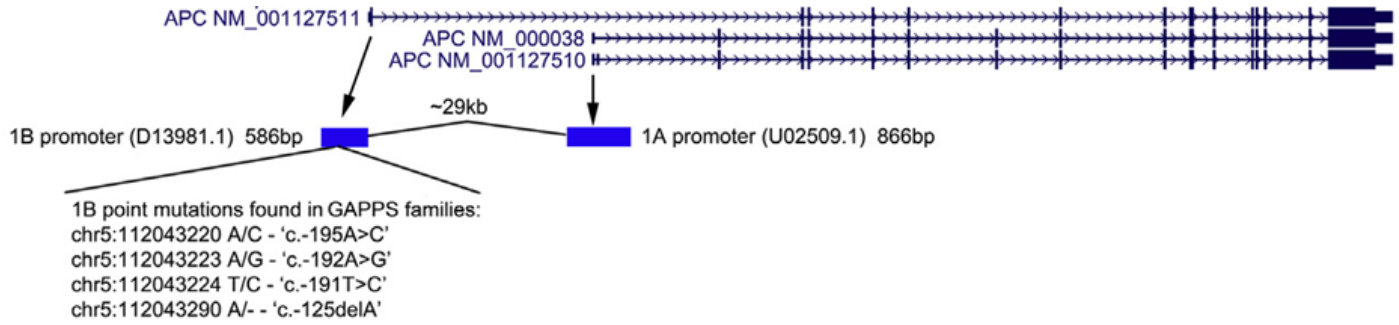
Etiology:



APC has two promoters, 1B and 1A.

1B promoter: *APC* transcription in stomach AND colon

1A promoter: *APC* transcription in colon



Het. variants disrupting *APC* promoter 1B cause gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) without colon polyposis

Familial Adenomatous Polyposis (FAP) – Genetic Testing

Indications for genetic testing (NCCN guidelines):

≥20 adenomas (consider if 10-19)
Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
Cribriform-morular variant papillary thyroid cancer
Consider it desmoid tumor, hepatoblastoma, unilateral CHRPE
Family history of polyposis and unable to test family member

Familial Adenomatous Polyposis (FAP) – Management

Colorectal cancer:

- Colonoscopy every year starting age 10-15
- Proctocolectomy or colectomy
- Continued surveillance after proctocolectomy/colectomy depending on surgical approach

Duodenal/gastric cancer:

- EGD starting age 20-25

Thyroid cancer:

- Ultrasound starting in teenage years every 2-5 years

Multiple Endocrine Neoplasia (MEN) and Familial Medullary Thyroid Cancer Syndromes (FMTC)

Inheritance: Autosomal Dominant (AD)

	MEN1	MEN2A/MEN2B/FMTC	MEN4
Gene	*MEN1*	*RET*	*CDKN1B*
Mechanism of action	Loss-of-function	Gain-of-function	Loss-of-function
Parathyroid tumors	90% risk	20-30% (mainly MEN2A)	55-80%
Pituitary tumors	Prolactinoma: 60% GH-secreting: 25% Other	N/A	30-45% (Prolactinoma, ACTH-secreting, GH-secreting)
Endocrine gastropancreatic tumors	Gastrinoma: 40% Insulinoma: 10% Other	N/A	Gastrinoma: 5-8% Non-functioning: 9-17%
Carcinoid	~10%	N/A	4-7%
Adrenocortical (cortisol/aldosterone)	40%	N/A	4-7% (Cortisol)
Pheochromocytoma	<1%	50% (except 0% for FMTC)	
Medullary thyroid carcinoma	N/A	100%	
Other		Marfanoid (MEN2B)	