8th Lynch Syndrome Education Night

September 25, 2019

TWITTER hashtag #ZCCeducationnight

Sinai Health System

Mount Sinai Hospital | Bridgepoint | Circle of Care | Lunenfeld-Tanenbaum Research Institute

Hot Topics in Lynch Syndrome

Presented By The Genetic Counsellors

New Cancer Risks for Lynch Syndrome

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Lynch Syndrome Management - FAQs

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Carrier Testing and Reproductive Technology

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Sinai Health System Zane Cohen Centre for Digestive Diseases

ARTICLE | Genetics inMedicine

Open

Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database

A full list of authors and affiliations appears at the end of the paper.

Dominguez-Valentin et al. Genet Med. 2019 Jul 24. [Epub ahead of print]

Colorectal & Gynecologic Cancers

		MLH1		*MSH2*		*MSH6*		*PMS2*	Gen Pop
Organ	**Age**	Female	Male	Female	Male	Female	Male	Both	Both
Colorectal	30	0	4.5	1.9	2.6	0	0	0	
	40	11.8	16.4	6.9	9.9	2.5	6.3	0	
	50	20.8	33.6	16.9	18.1	4.4	6.3	0	
	60	32.2	45.2	26.2	34.1	8.9	8.9	0	
	70	44.1	52.8	41.9	46.3	20.3	11.7	3.4	
	75	**48.3**	**57.1**	**46.6**	**51.4**	**20.3**	**18.2**	**10.4**	**6.3**
Endometrial	30	0		0		0		0	
	40	1.9		2.3		2.3		0	
	50	14.7		17.5		12.6		0	
	60	27.3		38		28.3		9.3	
	70	35.2		46.5		41.1		12.8	
	75	**37**		**48.9**		**41.1**		**12.8**	**3.1**
Ovarian	30	0		0		0		0	
	40	2		2.2		2.3		0	
	50	6.1		10.5		2.3		0	
	60	10.1		12.6		2.3		3	
	70	11		17.4		10.8		3	
	75	**11**		**17.4**		**10.8**		**3**	**1.3**

Other LS-Associated Cancers

		MLH1		*MSH2*		*MSH6*		*PMS2*	Gen Pop
Organ	**Age**	Female	Male	Female	Male	Female	Male	Both	Both
Stomach, small bowel, bile duct, gallbladder, pancreas	30	0	0	0	0	0	0	0	
	40	1.2	0.8	0.8	0	0	0	0	
	50	1.8	2.1	2.1	1.2	0	0	2	
	60	4.5	5.1	5.1	7.1	0	4	2	
	70	8.4	15.7	15.7	15.9	1.7	4	3.6	
	75	**11**	**21.8**	**21.8**	**19.5**	**4.2**	**7.9**	**3.6**	**1.4**
Ureter & kidney	30	0	0	0	0	0	0	0	
	40	0.4	0	0	0	0	0	0	
	50	0.6	1	2.2	2.4	0	0	0	
	60	0.9	1.7	5.1	8.3	1.2	1.7	0	
	70	2.9	3.7	13.3	16.2	5.5	1.7	0	
	75	**3.8**	**4.9**	**18.7**	**17.6**	**5.5**	**1.7**	**3.7**	**1.5**
Bladder	30	0	0	0	0	0	0	0	
	40	0	0	0.6	0	0	0	0	
	50	0.3	0.6	2.1	1.6	0	4.3	0	
	60	1	2.2	3.2	6.1	1.2	4.3	0	
	70	2.7	4.6	6.8	8.7	1.2	4.3	0	
	75	**5.4**	**6.8**	**7.9**	**12.8**	**1.2**	**8**	**0**	**2.9**
Brain	30	0	0	0	0	0	0	0	
	40	0.4	0	0	0.7	0	0	0	
	50	0.6	0	0	1.1	0	0	0	
	60	0.9	0	0	1.9	1.2	0	0	
	70	1.6	0.7	0.7	3.7	1.2	1.8	0	
	75	**1.6**	**0.7**	**0.7**	**7.7**	**1.2**	**1.8**	**0**	**0.6**

Suggested LS-Associated Cancers

		MLH1		*MSH2*		*MSH6*		*PMS2*	Gen Pop
Organ	**Age**	Female	Male	Female	Male	Female	Male	Both	Both
Prostate	30		0		0		0	0	
	40		0		0		0	0	
	50		0.3		0.8		0	4.6	
	60		3.2		6.3		0	4.6	
	70		7		15.9		4.8	4.6	
	75		**13.8**		**23.8**		**8.9**	**4.6**	**11.3**
Breast	30	0		0		0		0	
	40	0.4		1.1		0		0	
	50	2.4		3.3		1.7		0	
	60	7		7.3		6.7		8.1	
	70	10.5		12.6		11.1		8.1	
	75	**12.3**		**14.6**		**13.7**		**15.2**	**12.1**

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Conclusions

- Cancer risks are highest for *MLH1* & *MSH2*
  - Men with *MLH1* higher risks than women
  - *MSH2* has higher extra-colonic/endometrial at older ages than *MLH1*
- Cancer risks lower in men with *MSH6* than women
  - Modest increased risk for CRC for both genders
  - Women had high risk for gynecologic cancers
- Cancer risk for *PMS2* not increased under age 50
  - Non-significant increase above age 50
- No significant increased risk of breast cancer for any gene
- Should screening recommendations change based on gene?

Lynch Syndrome Management

Frequently Asked Questions

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Q1: How Can I Reduce My Risk of Colorectal Cancer?

1. Regular Colonoscopies

- Colonoscopy every 1-2 years beginning at 20-25
  - Can help prevent CRC
  - Rationale: Polyp → cancer faster than sporadic
    Younger average age of colorectal cancer

    ❖ Might change in future based on gene and mutation-specific cancer risks

- FIT/FOBT tests and virtual colonoscopy are not replacements for colonoscopy for people with Lynch syndrome

Q1: How Can I Reduce My Risk of Colorectal Cancer?

2. Lifestyle/Environment

- Eat a Healthy Diet
  - Limit red meat & processed meats (nitrates/nitrites)
  - Eat Fibre, Dairy
- Reduce Alcohol Intake
- Don't Smoke

- Exercise More/Sit Less
  - Regular physical activity can lower your risk
  - Sedentary/sitting time increases your risk
- Lose weight
  - High BMI (being obese) increases your risk (Brenner et al., 2017)

http://www.cancer.ca/en/?region=on

Q1: How Can I Reduce My Risk of Colorectal Cancer?

3. Chemoprevention

- Aspirin
  - CAPP2 Trial - aspirin can reduce the risk of colorectal cancer in people with Lynch syndrome
    - High Dose: 600 mg (baby aspirin 81 mg) (Burn et al, 2011)
  - **CAPP3 Trial** – fine tuning the minimum effective dose
    - Stay tuned!!
- Vitamins
  - Decreased CRC risk associated with multivitamin and calcium intake for at least 3 years (Chau et al, 2016)

*****Speak to your doctor before taking any of the above*****

Q2: How Can I Avoid Insurance Discrimination?

- Genetic Non-Discrimination Act (GNDA)/Bill S-201
  - passed May 2017 in Canada
  - prohibits companies & employers from requiring genetic testing or requesting genetic results
  - prevents companies from denying services based on genetic results

Q2: How Can I Avoid Insurance Discrimination?

Some Limitations…..

- Insurance companies will ask about personal & family history of cancer
  - Having cancer yourself, or a strong family history of cancer might increase premiums anyways, regardless of genetic test results
- "Lynch syndrome" might be mentioned in other medical records, i.e. colonoscopy reports

→Some younger/unaffected individuals might consider getting insurance <u>before</u> genetic testing for familial mutation

Q3: At What Age Should My Children Have Genetic Testing?

- Age 18-20
  - Make own medical decisions
  - Colonoscopies start at 20-25
- Test <18 in rare circumstances
  - Very young colon cancer in family
  - Siblings want to get tested together
  - Both parents have Lynch syndrome (very rare)

→Talk to your genetic counsellor about strategies for discussing Lynch syndrome with your children

Q4: What Are The Updated Screening Recommendations for Lynch Syndrome?

- Guidelines haven't changed recently
  - But might in future
- Update your genetic counsellor with new cancers/polyps in family
- Screening summary
  - Share with your health care providers

Screening Recommendations for Lynch syndrome

Strongly recommended for your patient

Re: _____ DOB: _____

Site at Risk	Screening recommended	Frequency	Age to start	Strength of recommendation
Colorectum	Colonoscopy	Every 1-2 years	Begin at age 25 (or 2-5 years younger than a CRC diagnosis in the family under age 25)	Strongly recommended
	Colectomy (sub-total with ileal-sigmoid/rectal anastamosis) to be considered if CRC is identified or adenomatous polyps that cannot be managed through endoscopy			
Gastric/GE Junction	Forward-viewing EGD w biopsy to rule out *H. pylori*	Consider baseline screening and test for *H. pylori* which may increase risk *If familial clustering of gastric ca or for individuals of Asian descent the risk may be higher and more regular EGD screening may be considered.		Evidence is lacking - balance of benefits and harms cannot be determined.
Endometrium	Patient awareness of gyn. cancer symptoms so it can be investigated thoroughly Prophylactic TAH-BSO to be discussed after child-bearing is complete			Strongly recommended
	Pelvic and transvaginal ultrasound Endometrial biopsy	Annually	Begin at age 30-35 (or 10 years younger than any endometrial ca < age 35 in the family)	Evidence is lacking, the balance of benefits and harms have not been determined (Offer in research setting)
Ovarian	CA-125	Annually	Begin at age 30-35	
Urinary tract cancers (renal pelvis, ureter, bladder)	For *MSH2* positive families and those with familial clustering: Consider: Non-invasive: Urine cytology and microhematuria or Invasive: Cystoscopy - consult uro-oncologist	Annually (using 2 separate samples)	Begin at age 35 (or dependent on age of onset in the family)	Evidence is lacking - balance of benefits and harms cannot be determined
Skin: Sebaceous adenoma/carcinoma & keratoacanthomas	Self skin checks in all families Full body screening by dermatology if lesions are seen	Annually	After confirmation of skin lesion in patient or family	
Other cancers at lower risk: Small bowel, hepatobiliary tract (bile duct, pancreas), brain Breast, Prostate	Assess based on familial clustering and effectiveness of screening. Routine annual physical and population-based guidelines as required (PAP smear, mammogram, etc.)			Evidence is lacking for additional recommendation of screening Note: Side-viewing endoscopy not recommended in LS

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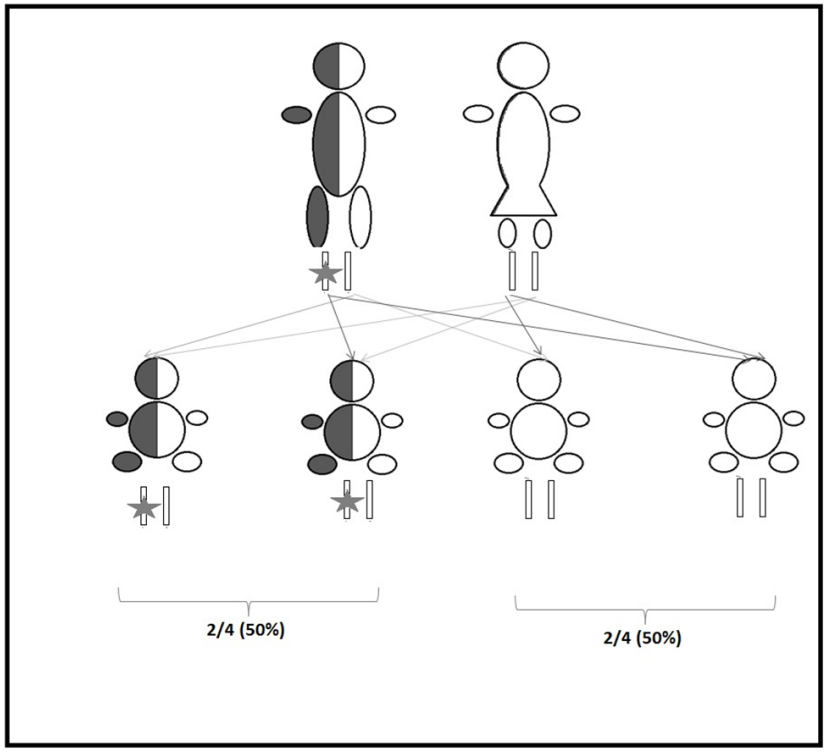
Inheritance of Lynch Syndrome



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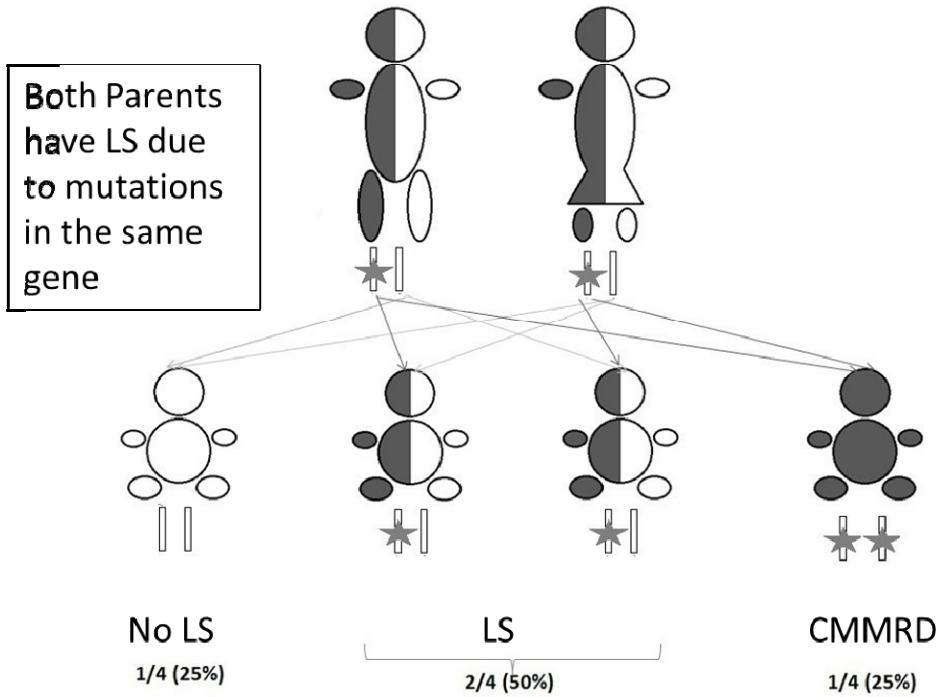
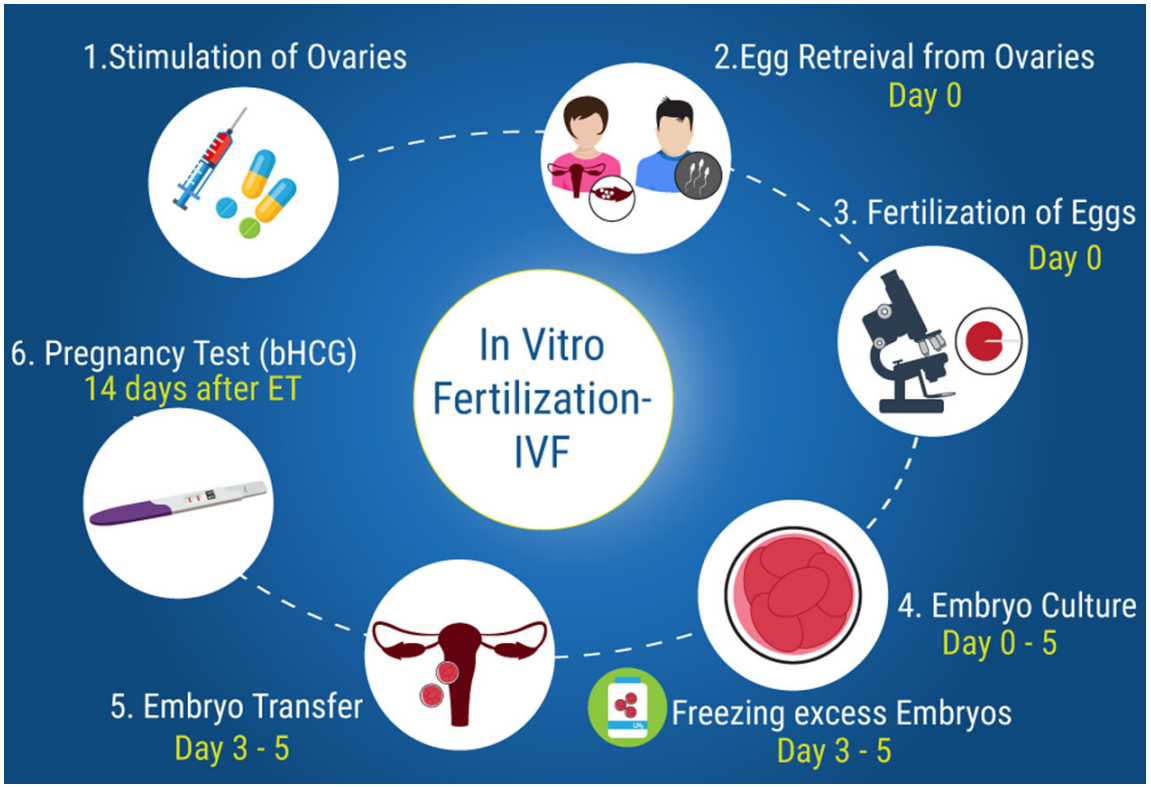
Inheritance of Constitutional Mismatch Repair Deficiency (CMMRD)



Updates to Testing Options

- "Carrier Testing" for mutations in the *MSH6* or *PMS2* genes is available for:
  - Partners of those with a mutation in one of these genes who are considering having children
  - Parents of young children whose other parent has a mutation in one of these genes
- This testing not necessary for those with older children
- Testing for partners of those with *MLH1/MSH2* mutations depends on if their family history is suggestive of LS

In Vitro Fertilization



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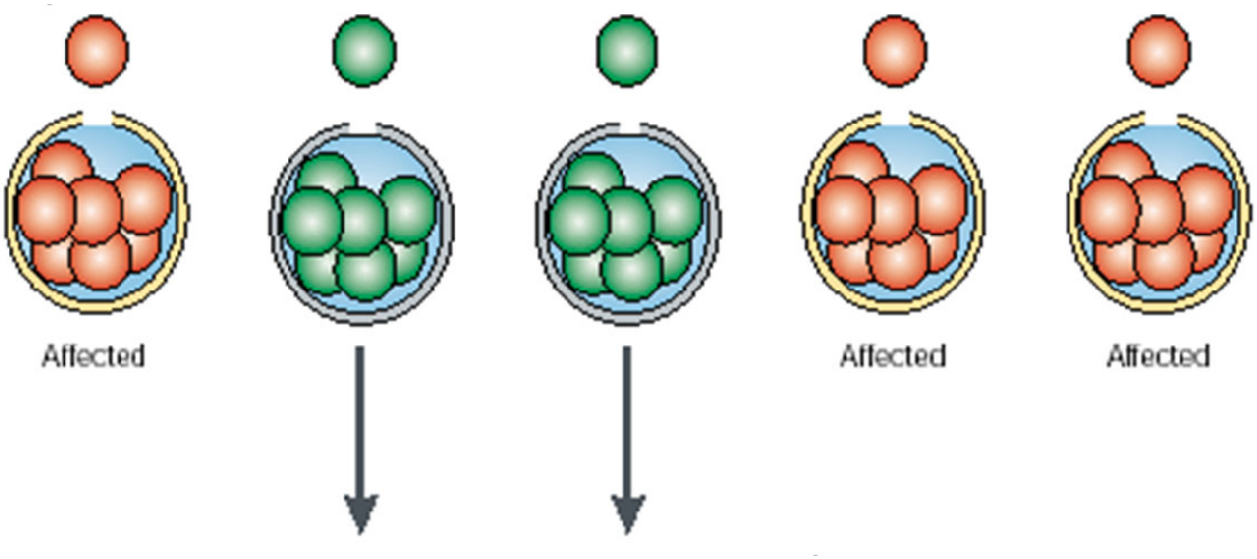
Preimplantation Genetic Testing (PGT-M)



Cost of PGT-M

- OHIP covers 1 round of IVF which otherwise costs approximately $8,500-10,000.
- OHIP does NOT cover the following:
  - Medication cost – approximately $4,000-5,000.
  - PGT-M cost – approximately $7,000-11,000.
  - Storage fees for embryos – approximately $100 per year

PGT-M Continued

- IVF and PGT-M do not guarantee that there will be any unaffected embryos
- This process cannot guarantee a healthy pregnancy