Application of Genetic testing to the management of Colon Polyps and Colon Cancer

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Gastroenterologist at
Mashhad , Iran

Scientific manager :Dr Ladan goshayeshi

speakers:

- **Dr ladan goshayeshi: Gastroenterologist**
- **Dr Abbaszadegan : geneticist**
- **Dr Majid Ansari : Colorectal surgeon**
- **Dr Lena goshayeshi : PHD in biotechnology ,post doc medical genetic .**

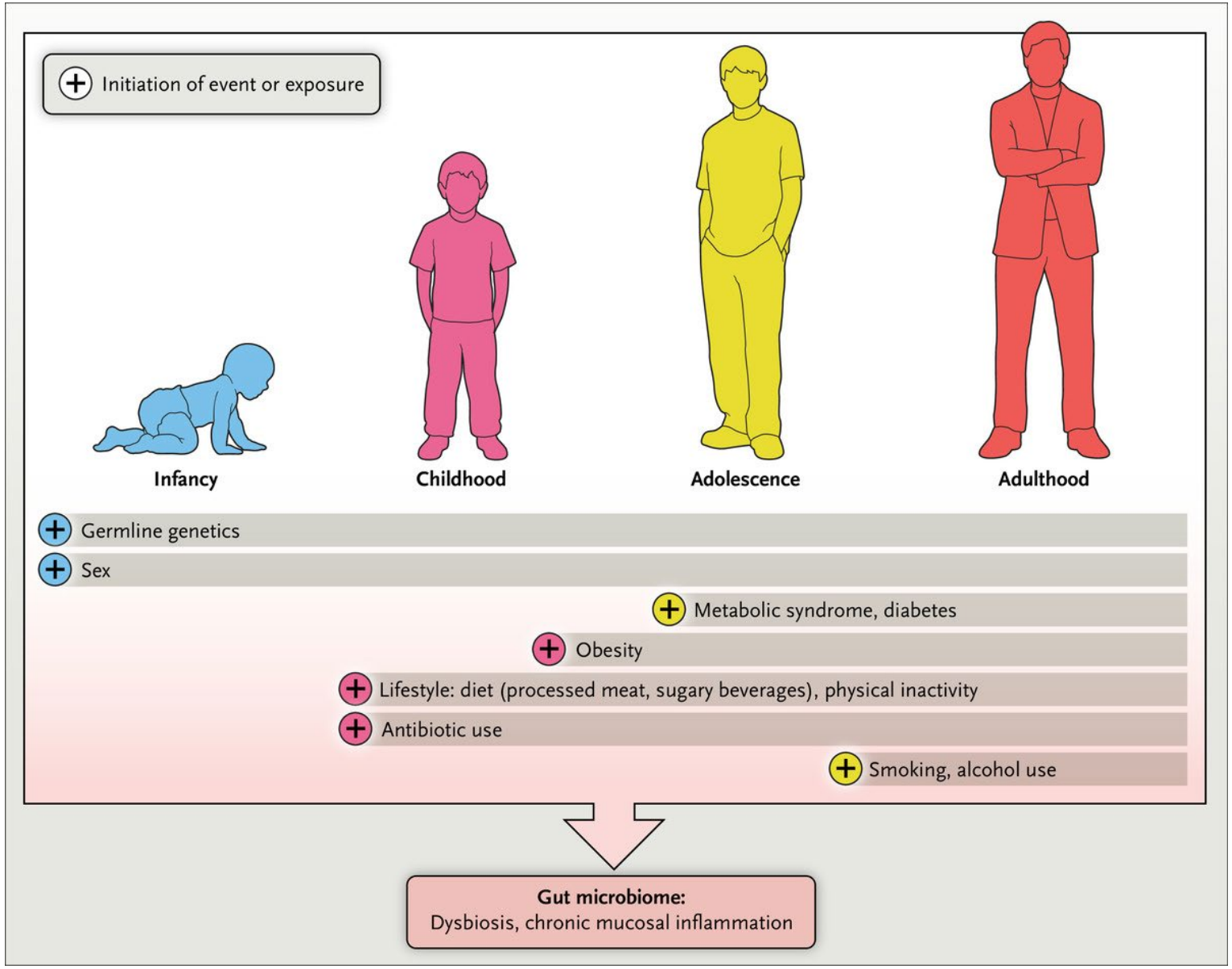


Number and ASR of top 5 cancers in Iran in 2016 Total population

Organ	Number	ASR (per 100,1000)
Breast	58689	36.45
Skin (non-melanoma)	44754	15.05
Colorectal	43580	14.49
Stomach	41865	13.82
Prostate	27218	18.87

Analysis of data of population-based cancer registries.
International Journal of Cancer. 2022 Dec

Factors Influencing the Risk of Colorectal Cancer

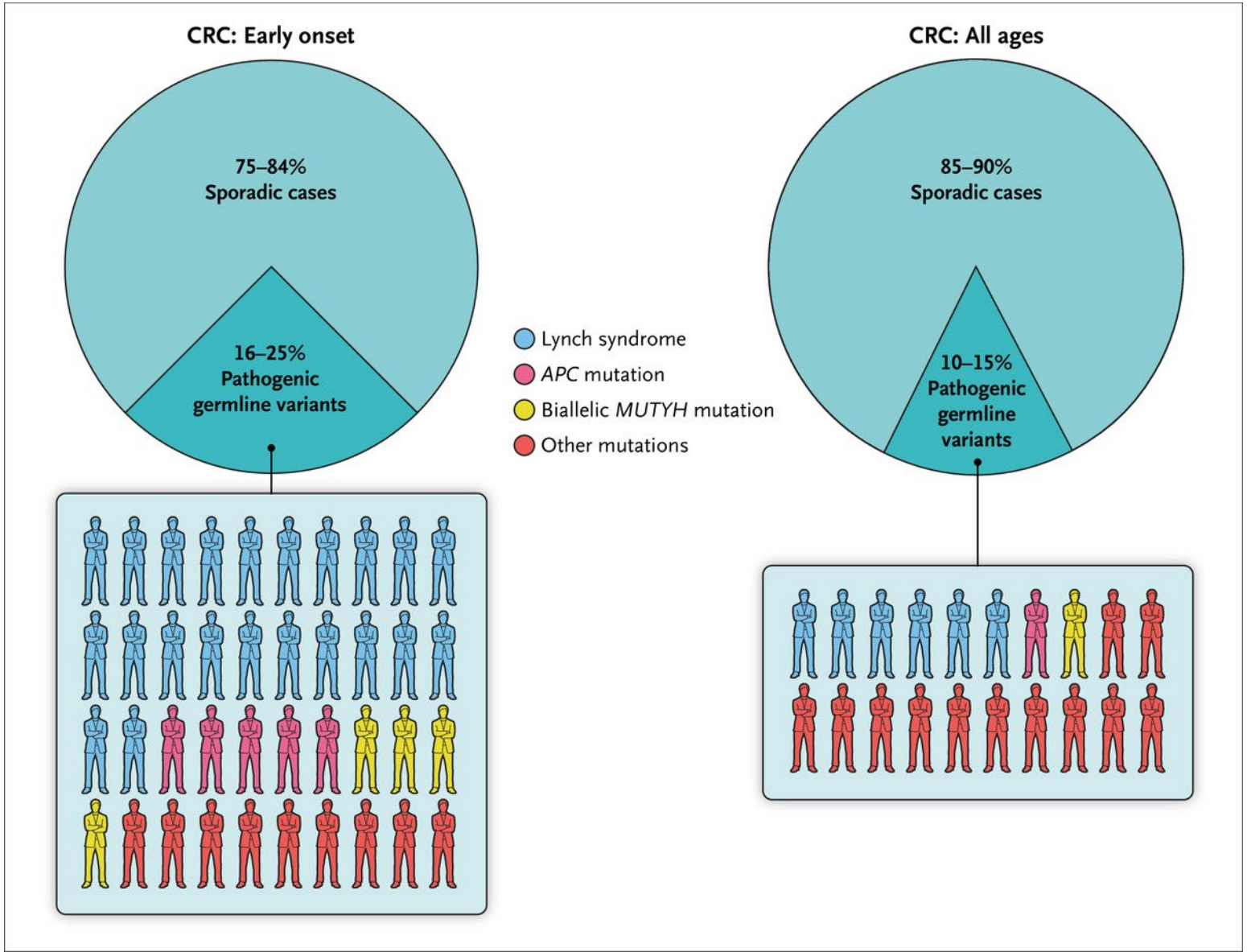




FA Sinicrope. N Engl J Med 2022;386:1547-1558.

The NEW ENGLAND JOURNAL of MEDICINE

Prevalence of Pathogenic Germline Variants in Patients with Colorectal Cancer (CRC)





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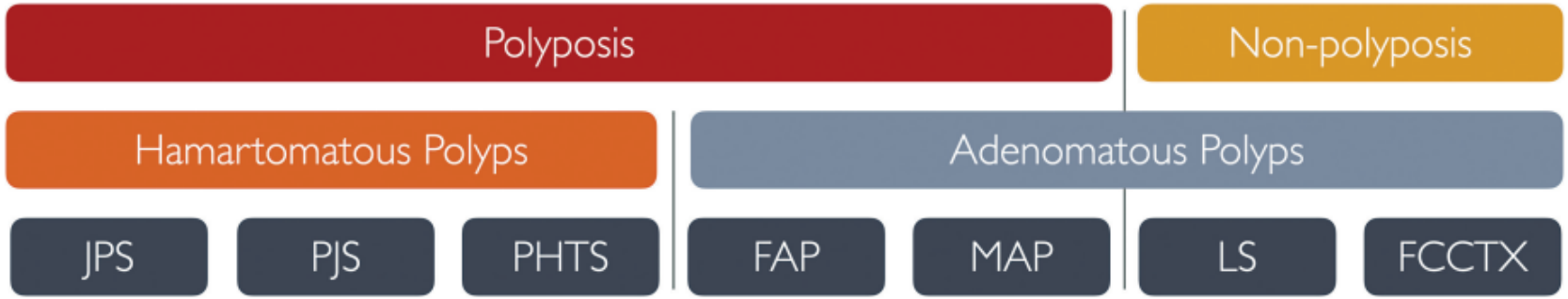
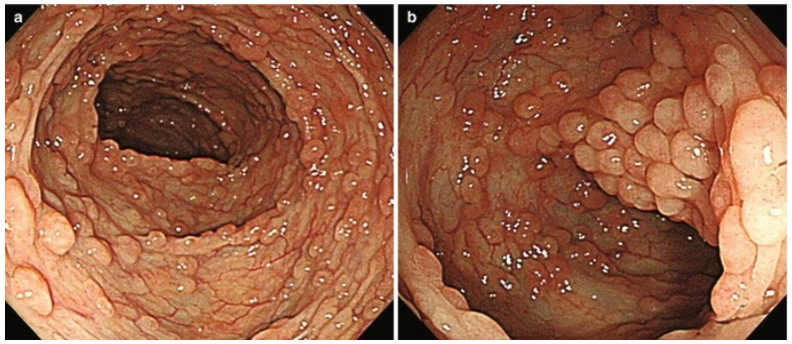
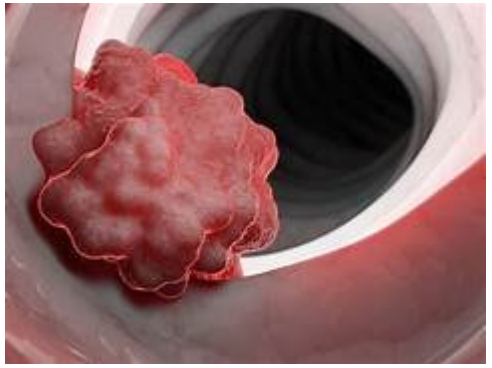


Fig. 1 Broad classification of hereditary colorectal cancer syndromes based on polyp histology. Note: Polymerase proofreading–associated polyposis (PPAP) and NTHL1-associated polyposis (NAP) are not included in this schematic but are rare adenomatous polyposis syndromes.





Clin Colon Rectal Surg 2025



well-characterized hereditary ectal cancer syndromes

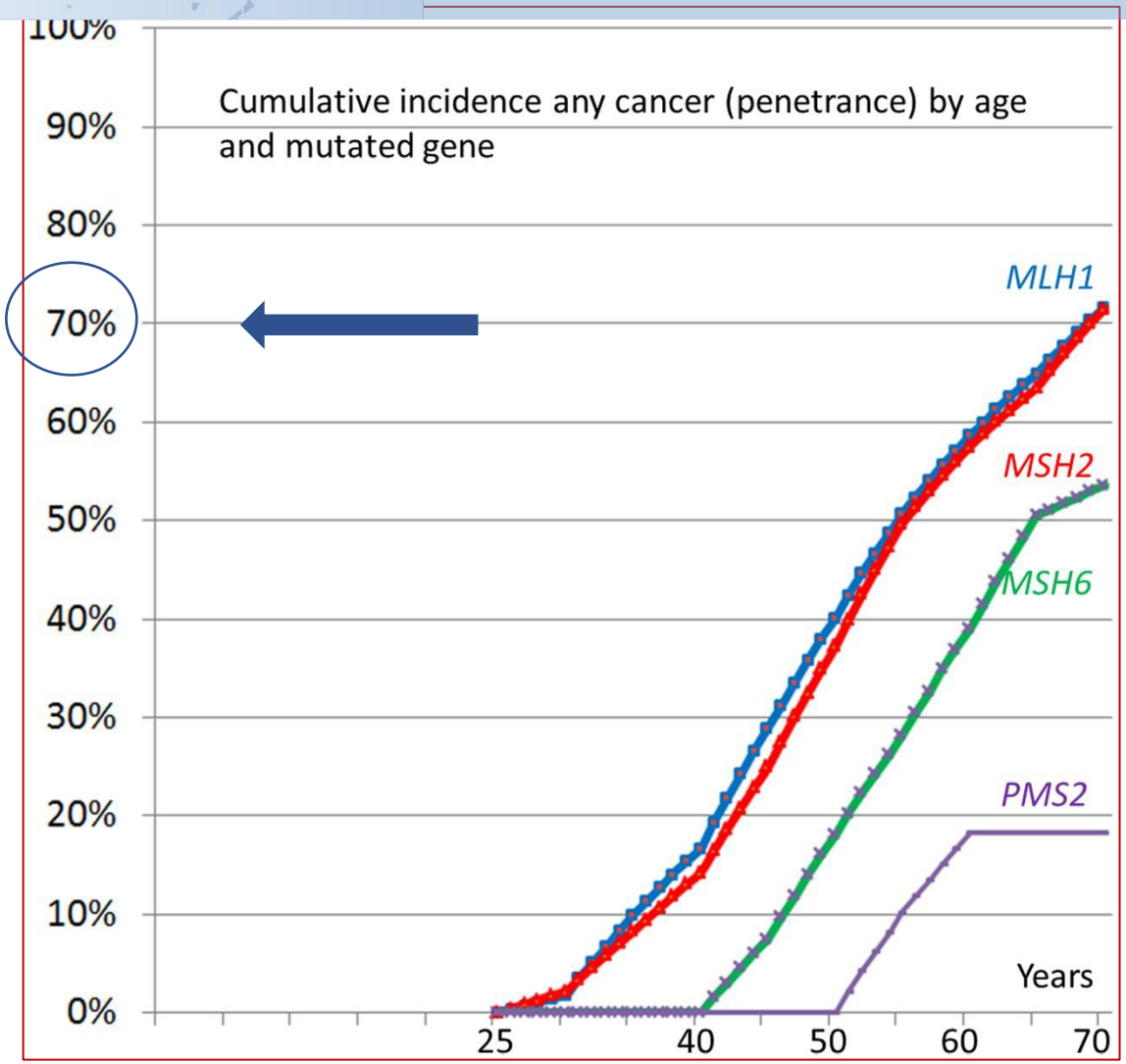
Lynch syndrome (LS) 3-5%

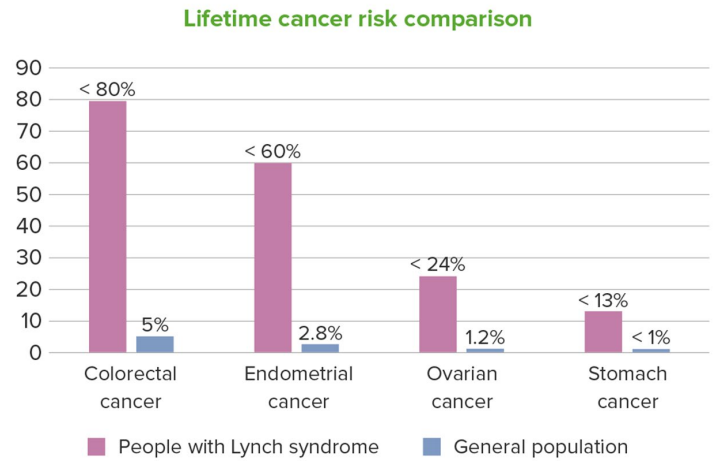
Colon polyposis :

- **Familial Adenomatous Polyposis (FAP) 1%**
- **MUTYH- Associated Polyposis (MAP)**
- **Polymerase Proofreading–Associated Polyposis (PPAP) caused by POLE or POLD1**

American college of medical genomics (ACMG) 2021 nature

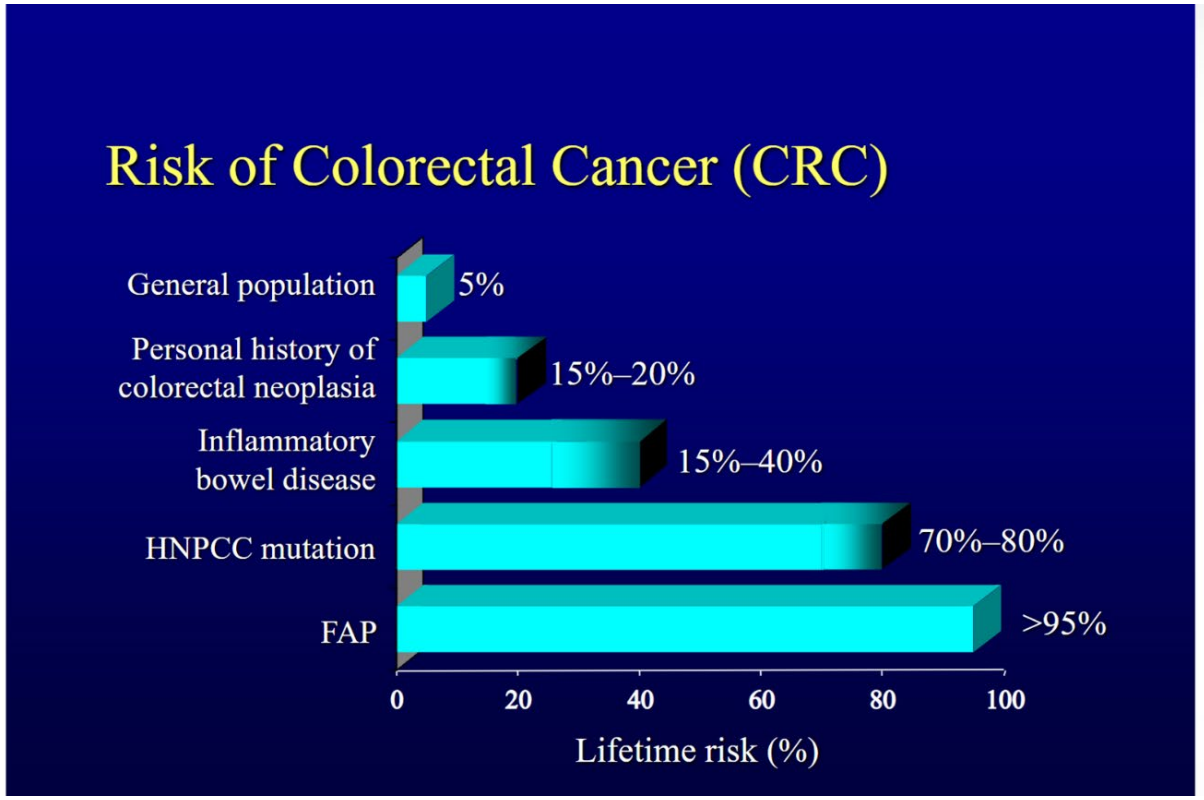
Calculated cumulative incidences by age and mutated gene for any cancer





Pål Møller et al. Gut 2017;66:464-472

CRC risk in Familial adenomatous polyposis syndrome (FAP)



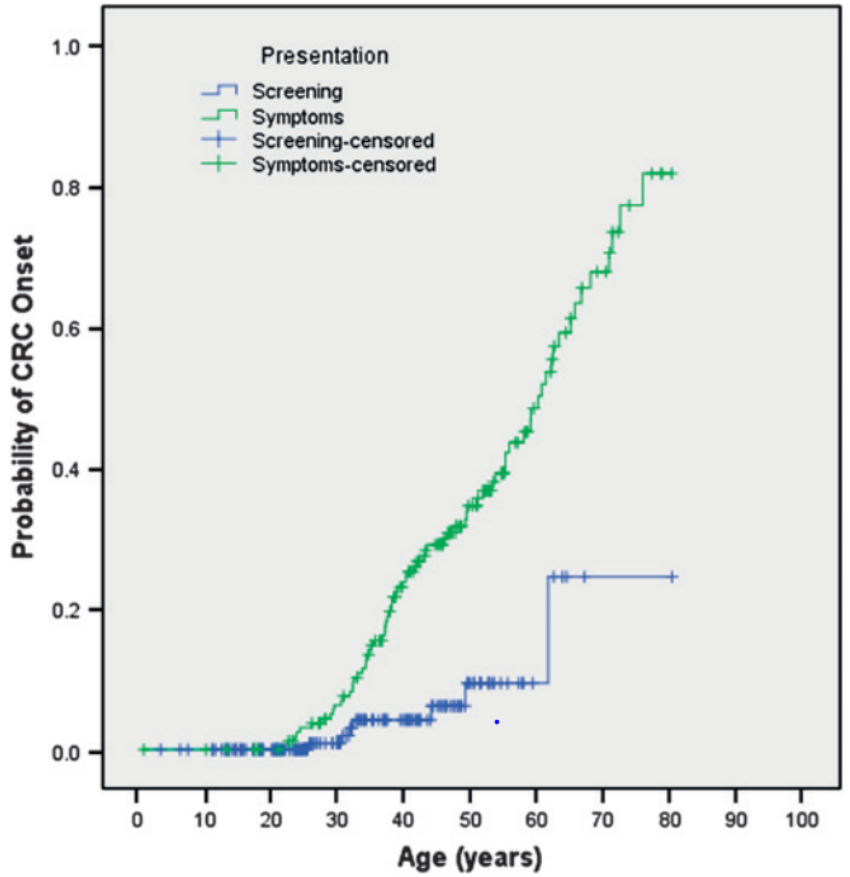


Figure 3 Kaplan-Meier survival curve to show the cumulative probability of familial adenomatous polyposis (FAP) patients developing colorectal cancer (CRC), of the screening population and the symptomatic population (χ^2=18.73, 1 df, p≤0.001, log rank test).

The impact of screening and genetic registration on mortality and colorectal cancer incidence in familial ,Gut 2010;

Prevention of colorectal cancer

Population screening by FIT

- Reduction of mortality by 10-20%
- Expensive

Screening of hereditary CRC

- Early identification reduces mortality by 60–80%.
- cheap



familial accumulation

early-onset of specific types of cancer.

develop multiple tumors

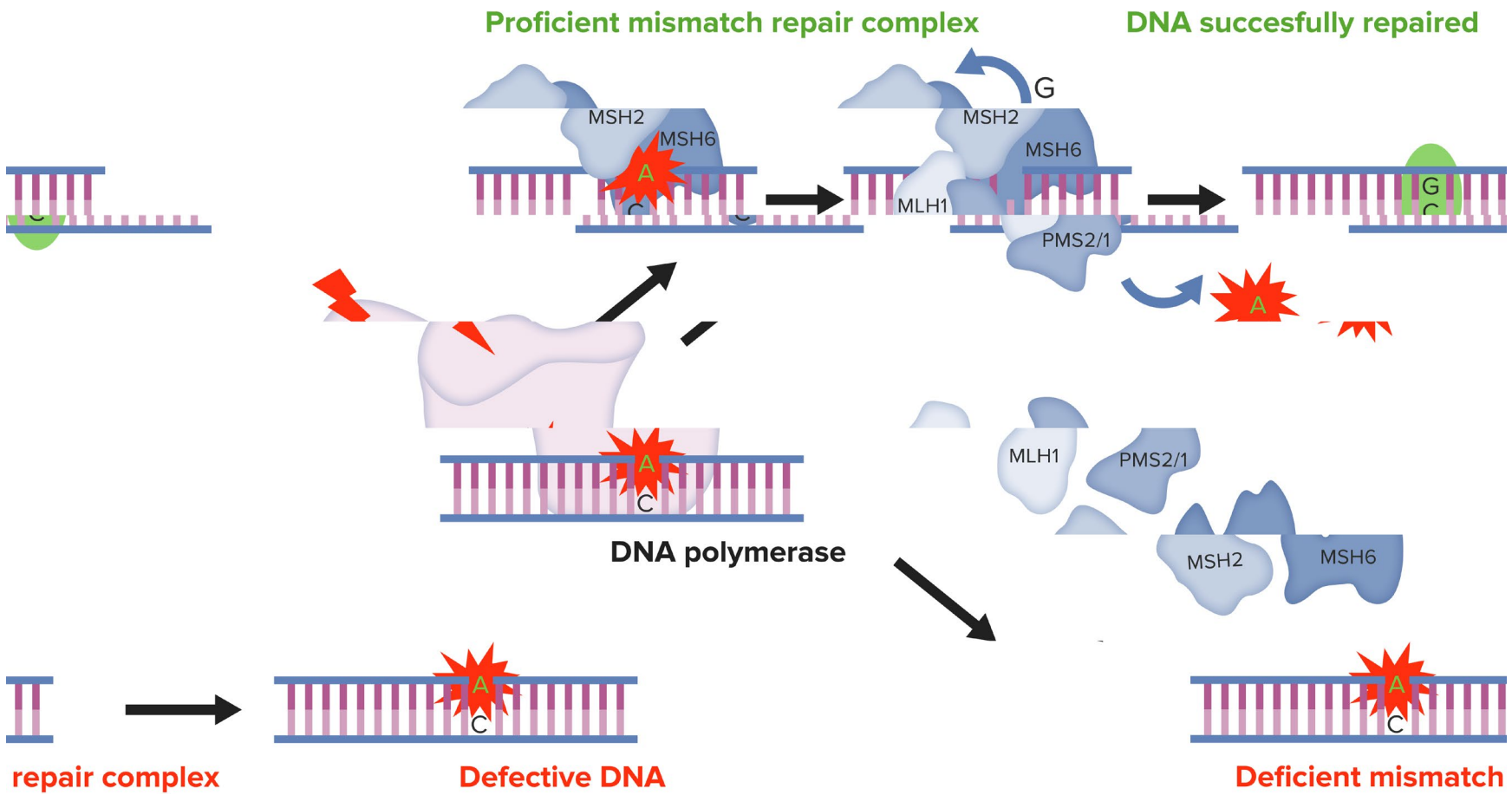


ing criteria for hereditary colorectal cer syndromes:

Lynch syndrome

colorectal polyposis syndromes

Lynch syndrome :



Lynch syndrome:

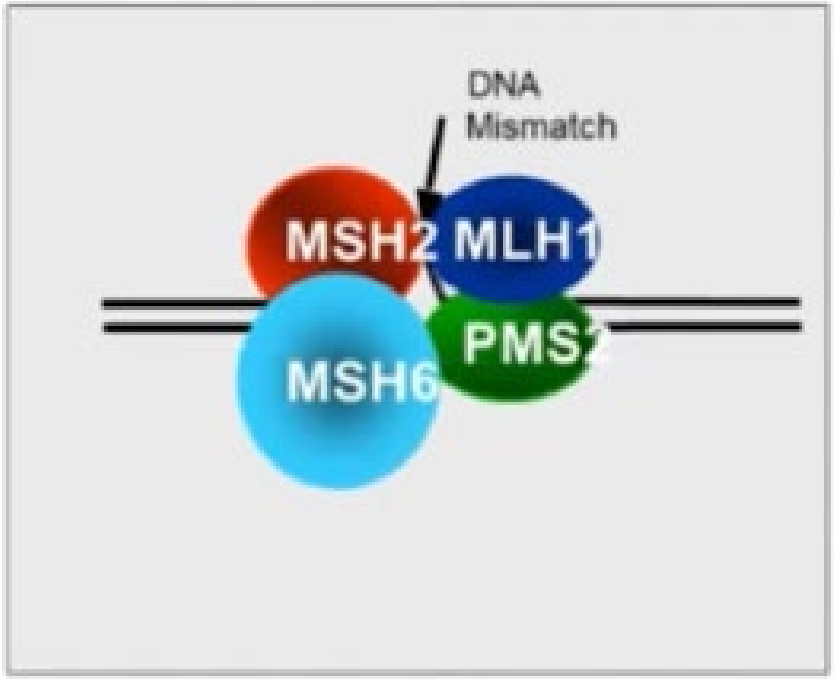
Defective DNA Mismatch Repair

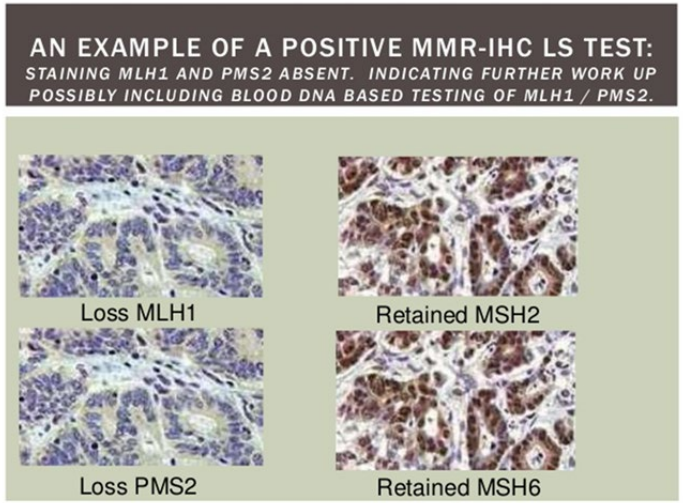
↓

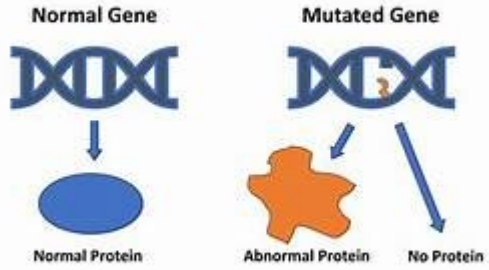
Accumulation of Mutations

↓

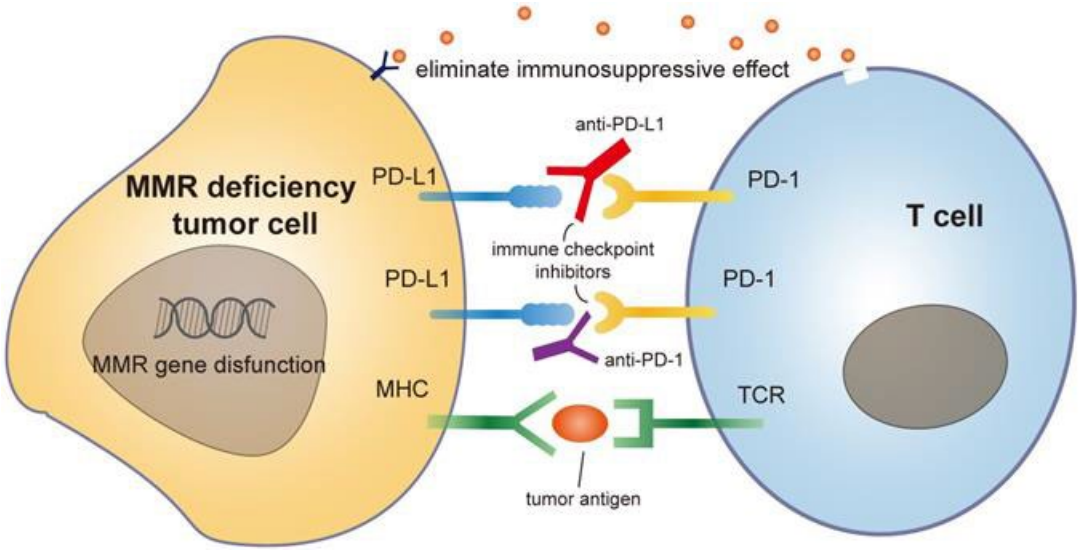
Accelerated progression to adenocarcinoma



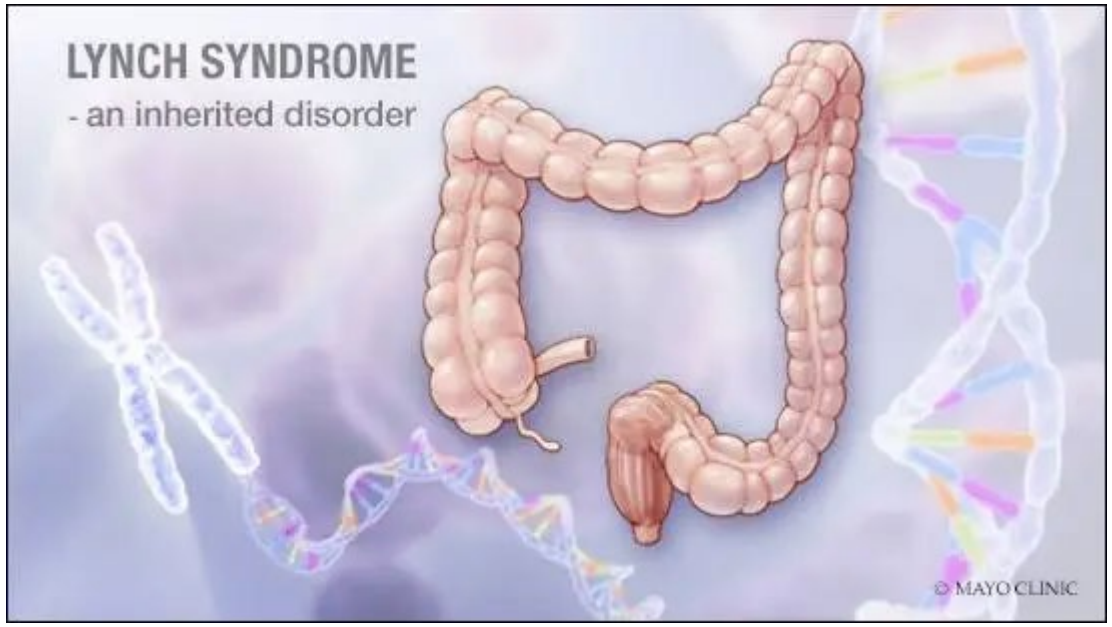




1-Defective DNA mismatch repair (MMR) occurs in approximately 15% of sporadic colorectal cancers (CRCs).Immunothereapy



2-More than 90% of colorectal from patients with Lynch syndrome have MSI and/or loss of an MMR protein



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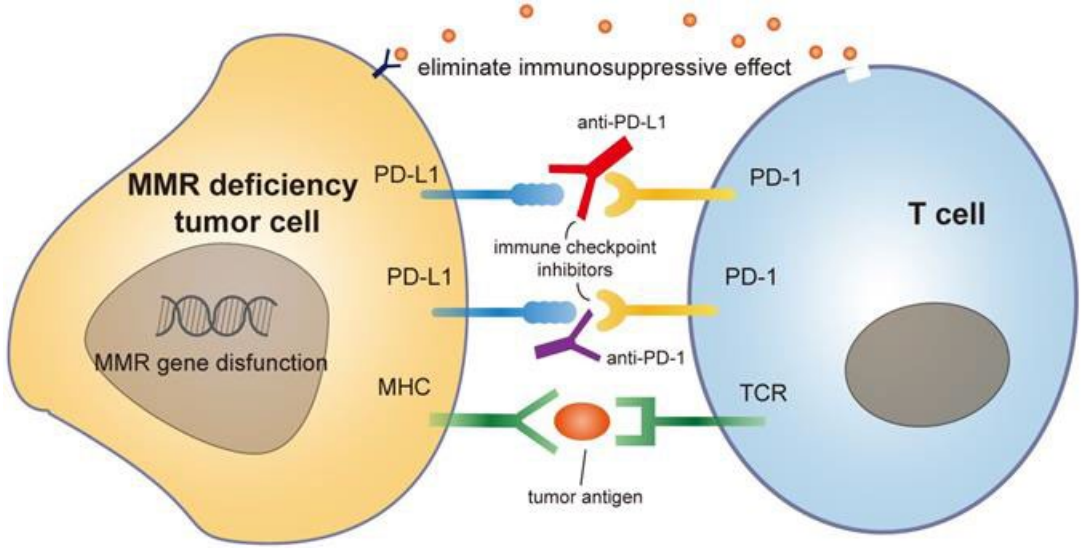
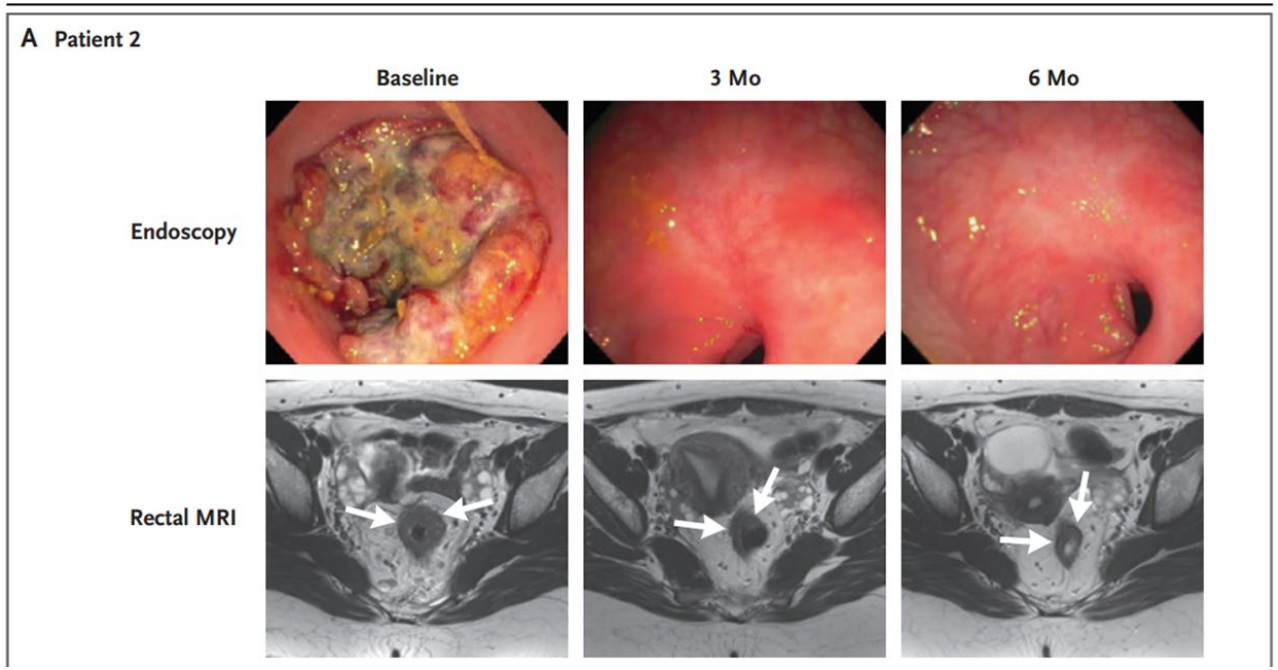
ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer





Immunothereapy

Selective strategy (clinical criteria)

Amsterdam II Criteria:
There should be at least 3 relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One individual should be a first-degree relative of the other 2
At least 2 successive generations are involved
At least 1 should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the CRC case(s) if any
Tumors should be verified through pathological examination

Revised Bethesda Criteria:
CRC diagnosed before age 50 years
Synchronous or metachronous colorectal or other Lynch syndrome–associated tumor
CRC with microsatellite instability–high histology (ie, presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed before age 60 years
CRC in a patient with a family history of Lynch syndrome–associated cancer diagnosed before age 50 years
CRC diagnosed in >1 relative with Lynch syndrome–associated cancer, regardless of age

Fig. 2 Clinical criteria that are often used to determine the need for Lynch syndrome testing. Note that some recommendations include germline testing for all colorectal cancer patients irrespective of clinical criteria.

Amsterdam II Criteria:

There should be at least 3 relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis)

One individual should be a first-degree relative of the other 2
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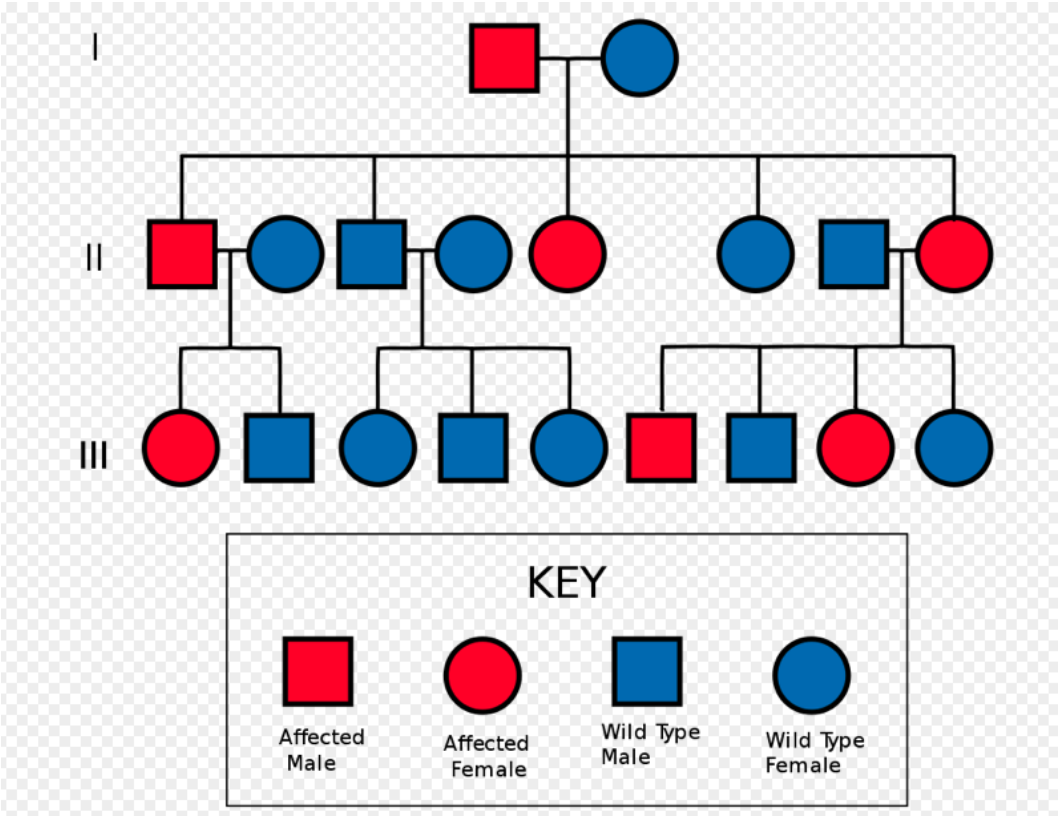

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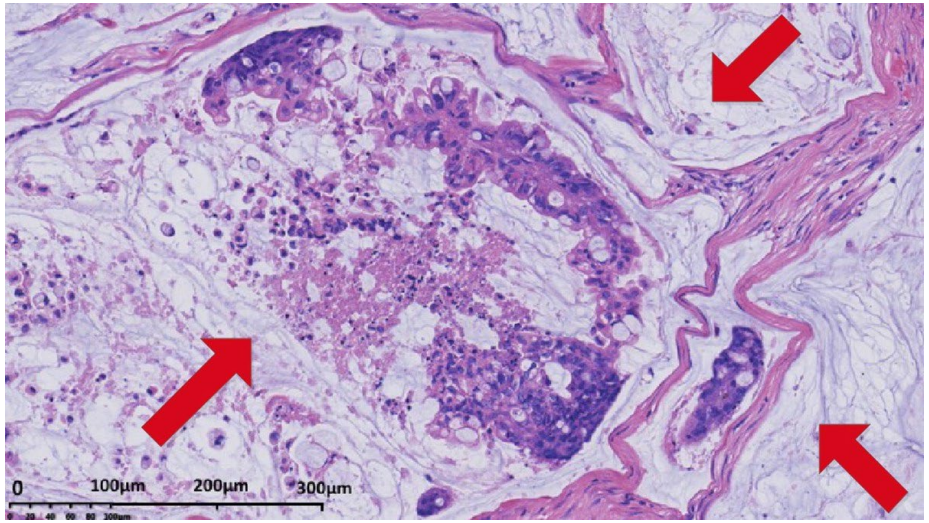
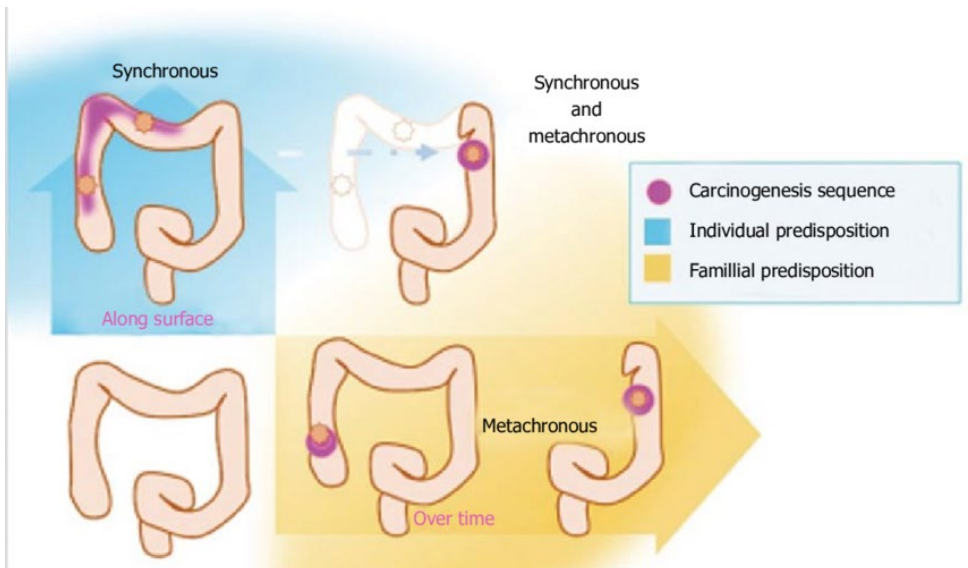
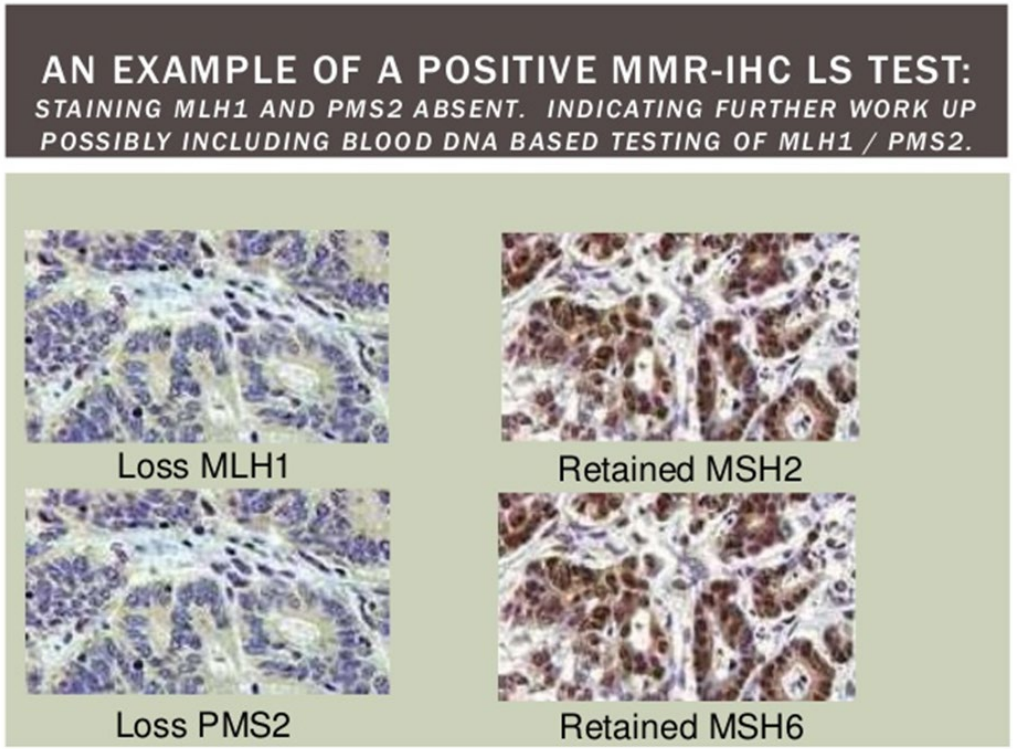




Universal screening for MMR deficiency

More than 90% of colorectal and other tumors from patients with Lynch syndrome have MSI and/or loss of an MMR protein

- **IHC for**
  - **MLH1,MHS2**
  - **MSH6,PMS2**
- **MSI**



American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology. 2015 Sep

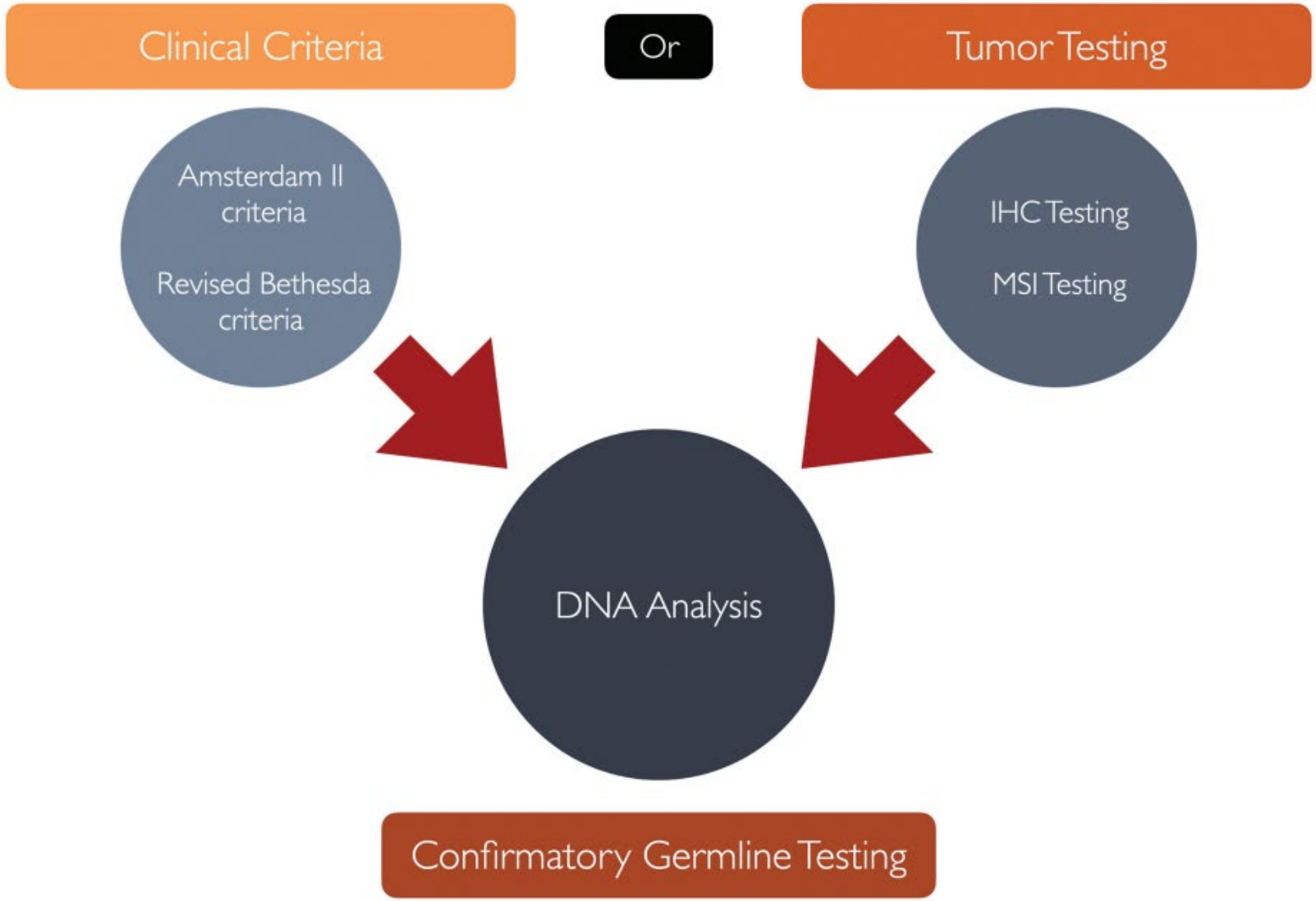


Fig. 3 Diagnostic approaches for non-polyposis syndromes.

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Testing criteria for Lynch syndrome:

The NCCN recommends

- **universal screening for MMR deficiency for all colorectal and endometrial tumors regardless of age at diagnosis**

However, in lower resource situations the following criteria may still be useful to help identify CRC patients whose tumors should be tested for MMR deficiency

- **the revised Bethesda criteria**
- **or Amsterdam II criteria**

Genetics in Medicine (2021)

Multigene panel testing using (NGS) or whole exome sequencing(WES)

- **overlapping phenotypes of the cancer syndromes**
- **Overcomes limited sensitivity of using clinical criteria alone**

Table 1. Genes associated with hereditary colorectal cancer (HCC) and/or polyposis recommended for multigene panel testing.

Gene symbol	Gene MIM	Chromosome locus	Reference sequence	Phenotype	Mode of inheritance
High risk genes					
APC	611731	5q22.2	NM_000038.5	FAP/attenuated FAP	AD
BMPR1A	601299	10q23.2	NM_004329.2	Juvenile polyposis syndrome and Hereditary mixed polyposis syndrome	AD
EPCAM	185535	2p21	NM_002354.2	Lynch syndrome	AD
MLH1	120436	3p22.2	NM_000249.5	Lynch syndrome; Muir–Torre syndrome	AD
MSH2	609309	2p21-p16	NM_000251.1	Lynch syndrome; Muir–Torre syndrome	AD
MSH6	600678	2p16.3	NM_000179.2	Lynch syndrome	AD
MUTYH+	604933	1p34.1	NM_1048171.1	*MUTYH*-associated polyposis	AR
PMS2	600259	7p22.1	NM_000535.5	Lynch syndrome	AD
PTEN	601728	10q23.31	NM_000314.6	*PTEN* tumor/hamartoma syndrome (also known as Cowden syndrome/ Bannayan–Riley–Ruvalcaba syndrome)	AD
SMAD4	600993	18q21.2	NM_005359.5	Juvenile polyposis syndrome (JPS); JPS/ hereditary hemorrhagic telangiectasia syndrome	AD
STK11	602216	19p13.3	NM_000455.4	Peutz–Jeghers syndrome	AD
Risk genes					
ATM[a]	607585	11q22.3	NM_000051.3	CRC susceptibility	AR
AXIN2	604025	17q24.1	NM_004655.3	Oligodontia–colorectal cancer syndrome	AD
BLM[a]	604610	15q26.1	NM_000057.3	CRC susceptibility	AR
GREM1	603054	15q13.3	NM_013372.6	Hereditary mixed polyposis syndrome	AD
MLH3	604395	14q24.3	NM_001040108.1	Lynch syndrome	AD
MSH3[b]	600887	5q14.1	NM_002439.4	FAP	AR
NTHL1[b]	602656	16p13.3	NM_002528.6	FAP	AR
POLD1	174761	19q13.33	NM_002691.3	Polymerase proofreading–associated polyposis	AD
POLE	174762	12q24.33	NM_006231.3	Polymerase proofreading–associated polyposis	AD
Genes associated with hereditary cancer syndrome where CRC/polyposis are possible manifestations					
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FLCN	607273	17p11.2	NM_144997.6	Birt–Hogg–Dubé syndrome	AD
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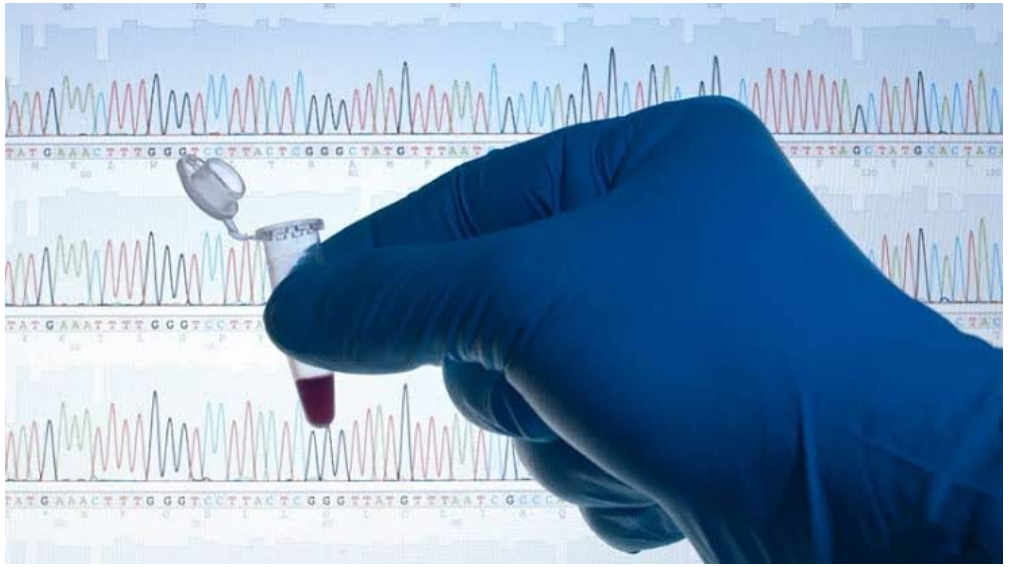
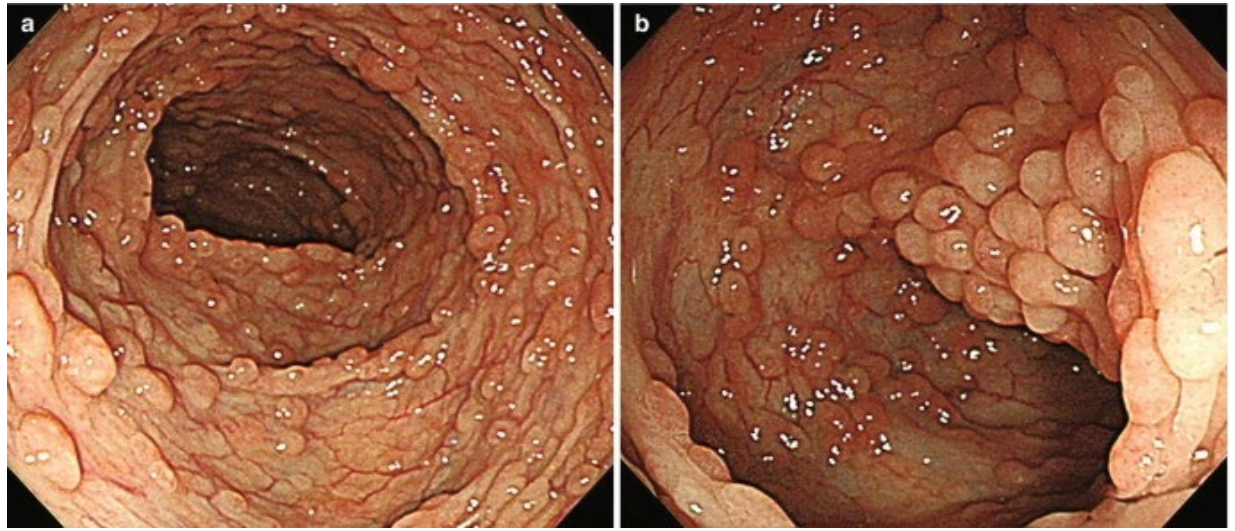
AD autosomal dominant, *AR* autosomal recessive, *CRC* colorectal cancer, *FAP* familial adenomatous polyposis.
[a]Heterozygous pathogenic variant.
[b]Biallelic pathogenic variants.



the American College of Medical Genetics and Genomics 2021

Colon

- **When we refer the colon polyposis for genetic consult and genetic test?**



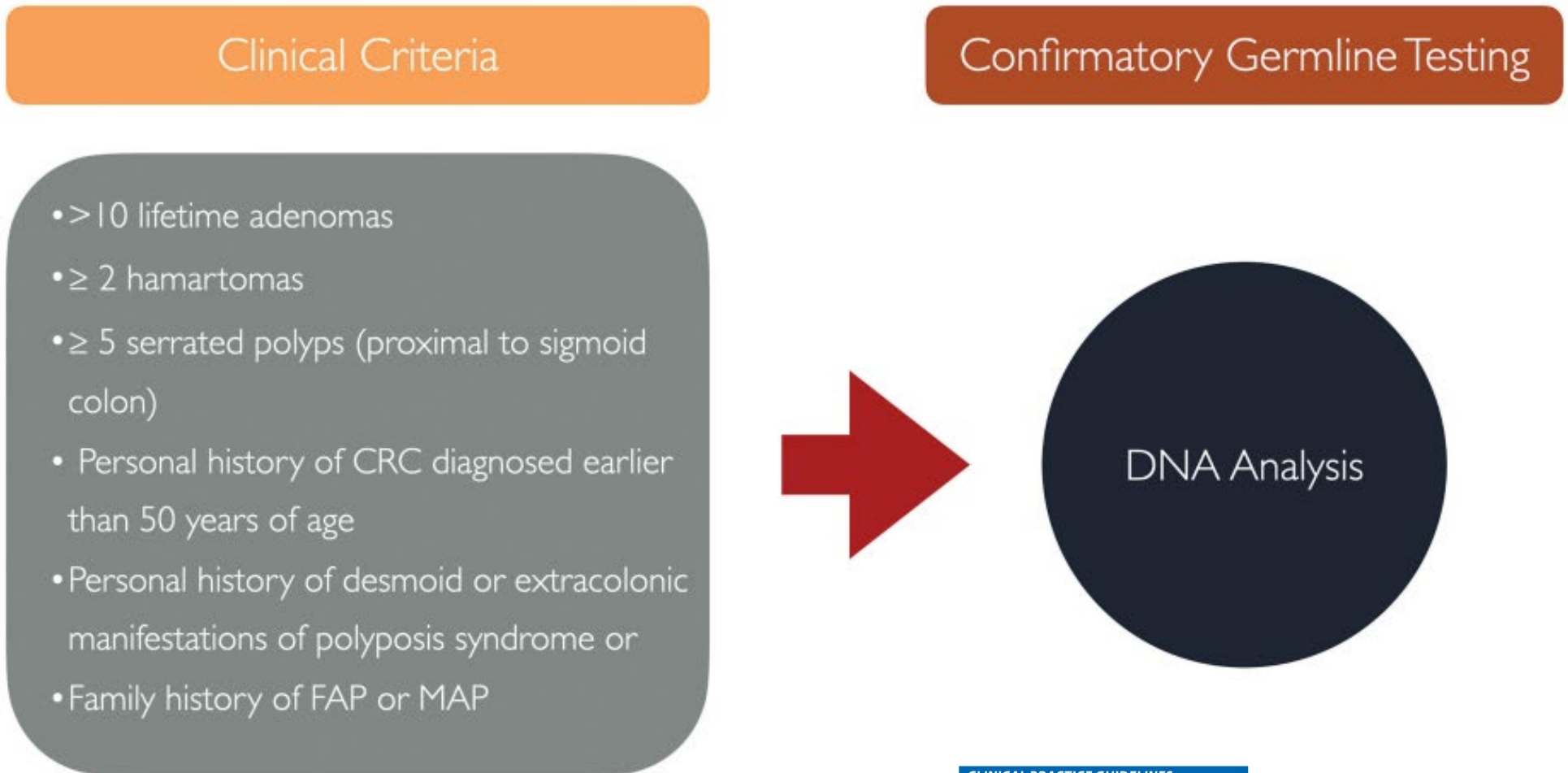


Fig. 4 Diagnostic approach for polyposis syndromes.

Multigene panel testing using (NGS) or whole exome sequencing(WES)

- **overlapping phenotypes of the cancer syndromes**
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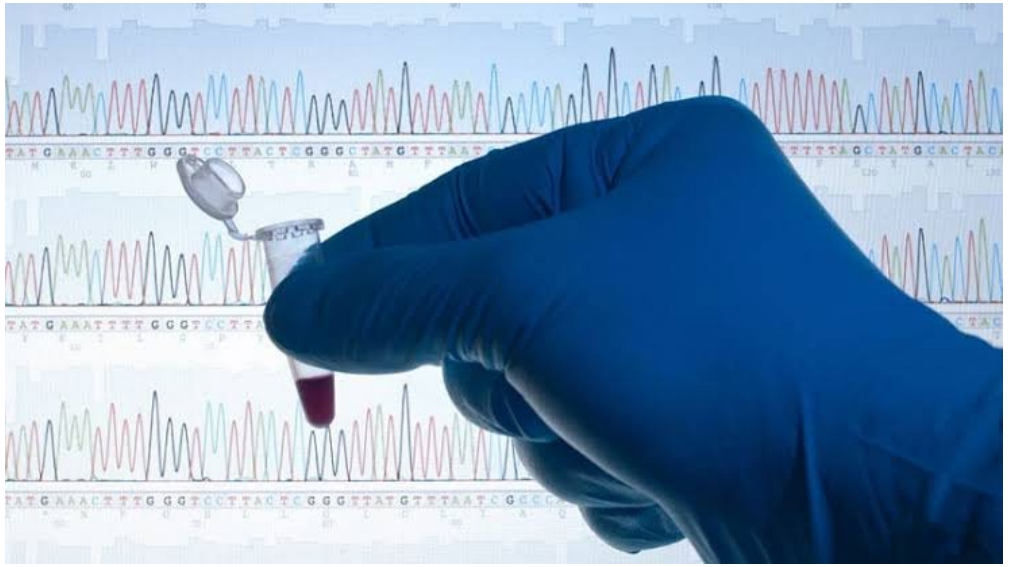

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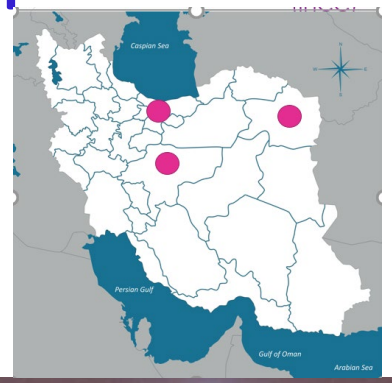
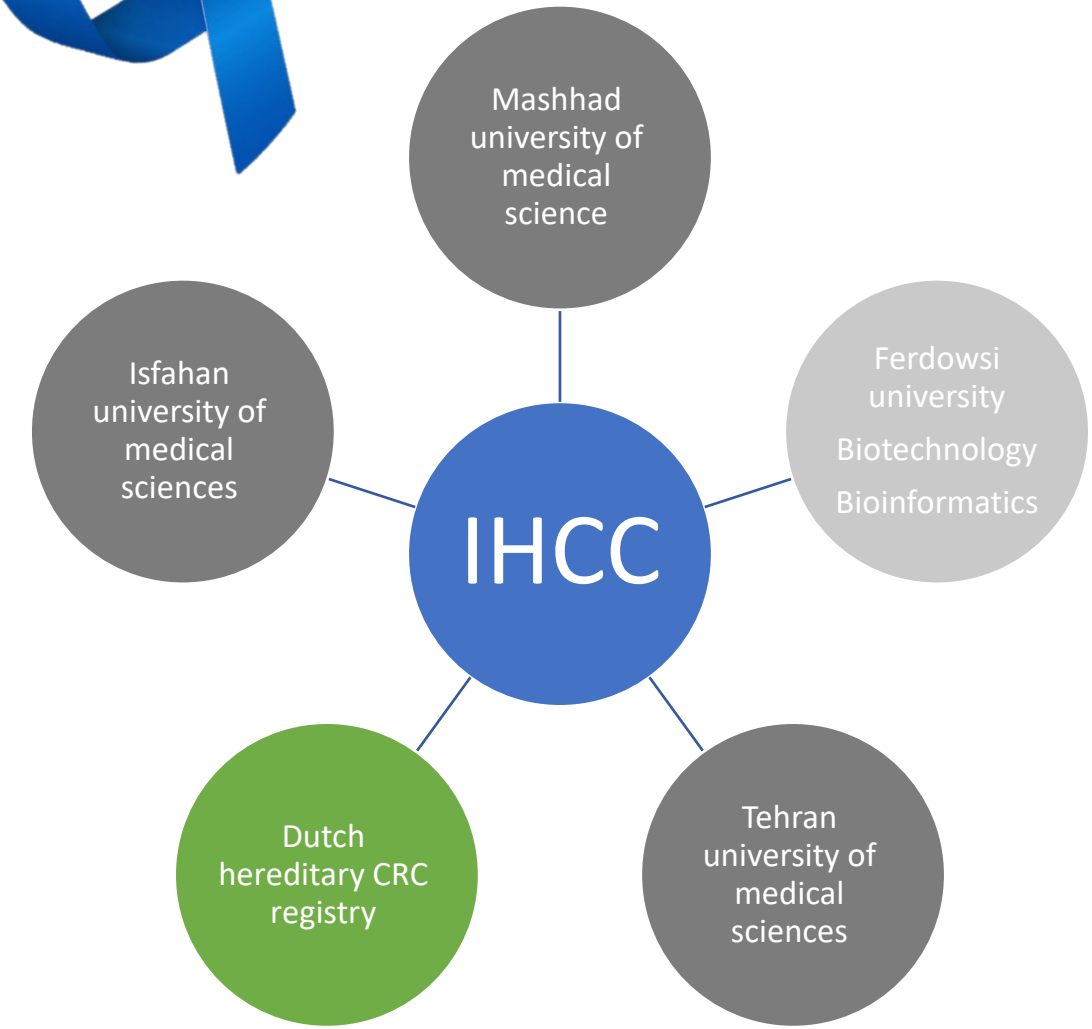
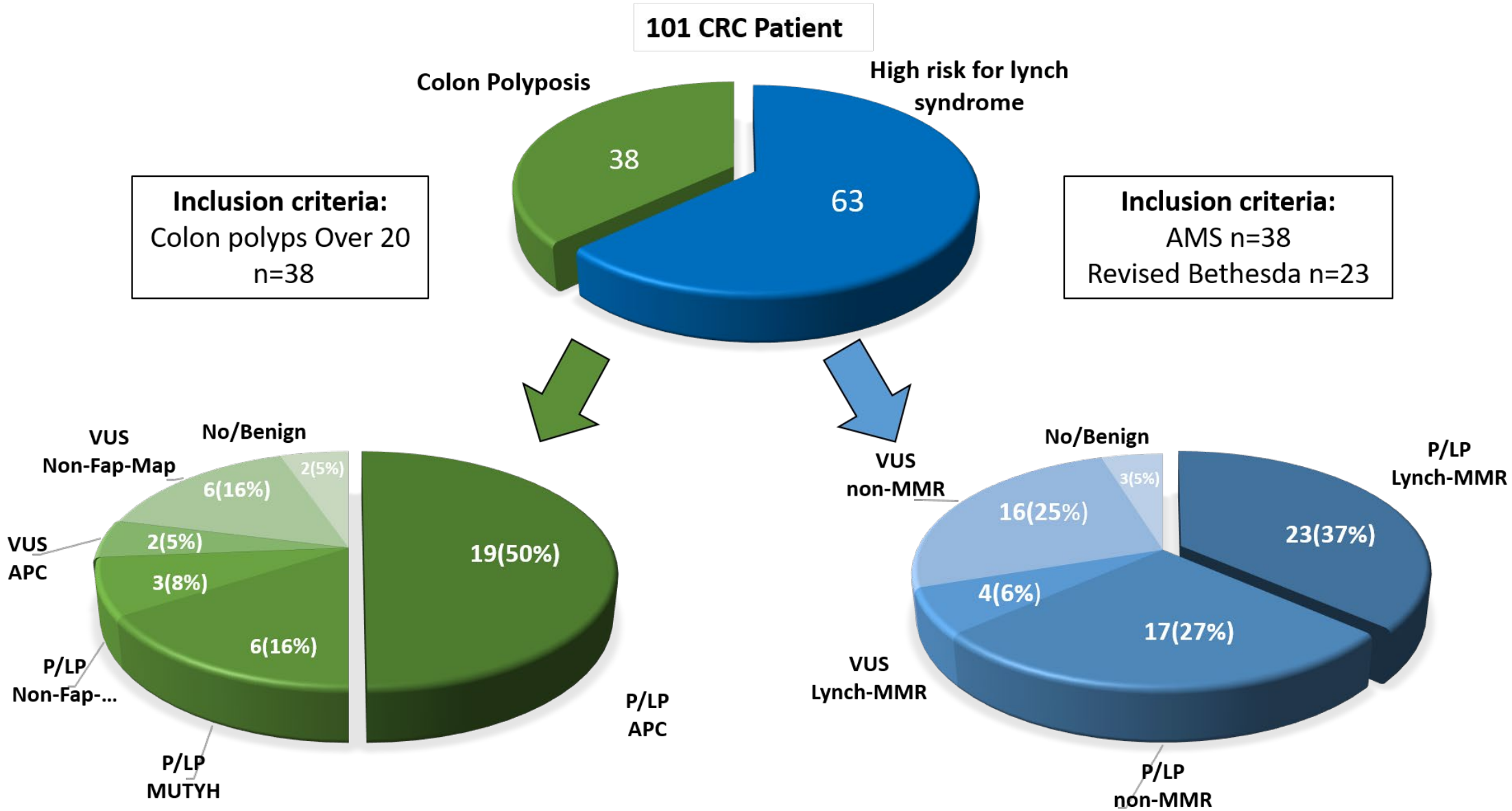
Iranian Hereditary colorectal cancer syndrome (IHCC), a multi-center program



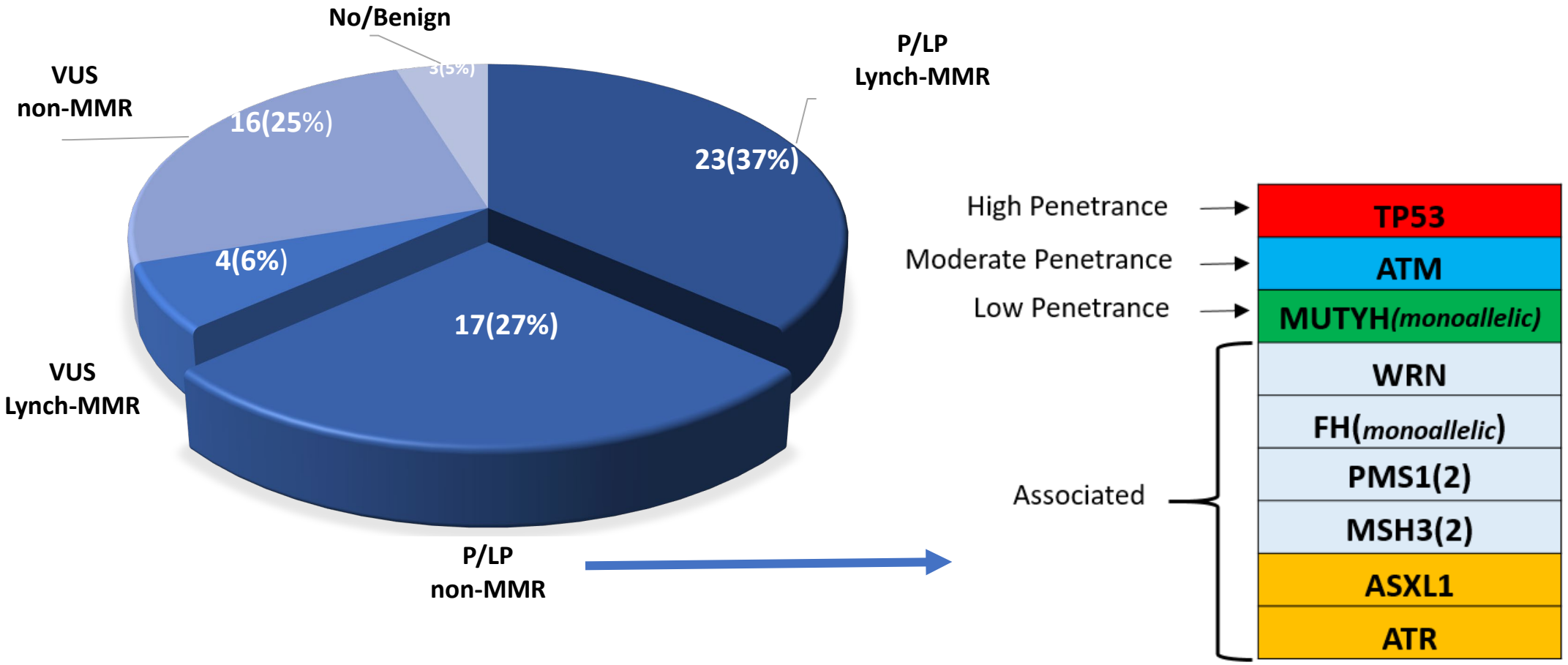







101 CRC Patient
Colon Polyposis
High risk for lynch syndrome
38
63
Inclusion criteria:
Colon polyps Over 20
n=38
Inclusion criteria:
AMS n=38
Revised Bethesda n=23
VUS
Non-Fap-Map
No/Benign
2(5%)
6(16%)
VUS
APC
2(5%)
3(8%)
19(50%)
6(16%)
P/LP
Non-Fap-...
P/LP
APC
P/LP
MUTYH
No/Benign
VUS
non-MMR
3(5%)
16(25%)
P/LP
Lynch-MMR
23(37%)
4(6%)
17(27%)
VUS
Lynch-MMR
P/LP
non-MMR

Lynch syndrome



Goshayeshi *et al. Cancer Cell International* (2025) 25:140
https://doi.org/10.1186/s12935-025-03773-3

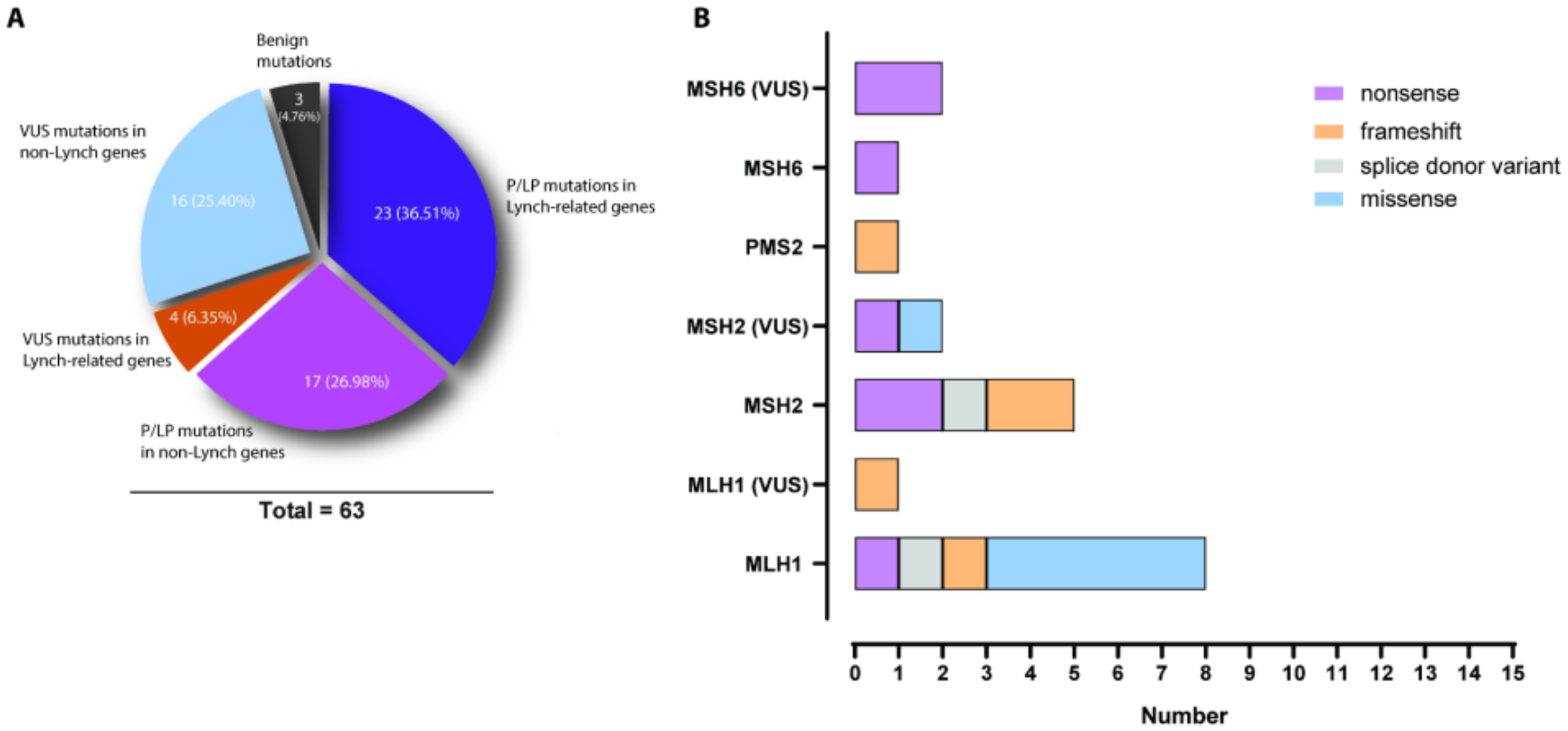
Cancer Cell International

RESEARCH Open Access

Germline variants in patients from the Iranian hereditary colorectal cancer registry

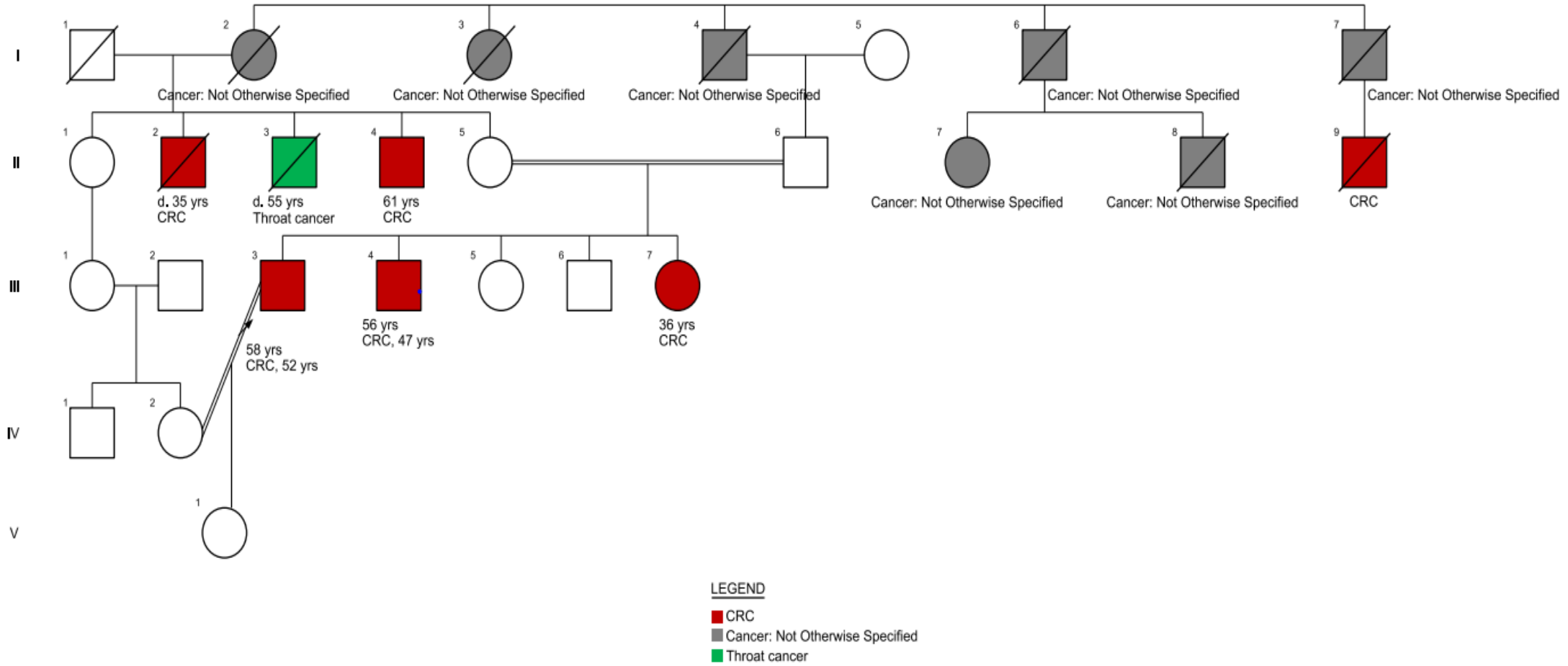
Lena Goshayeshi[1,2], Saeed Hoorang[3], Benyamin Hoseini[4], Mohammad Reza Abbaszadegan[5], Maryam Afrazeh[6], Maliheh Alimardani[5], Fatemeh Maghool[7], Milad Shademan[8], Morteza Zahedi[2], Mehrdad Zeinalian[9], Foroogh Alborzi[10], Mohammad Reza Keramati[11], Ashkan Torshizian[12], Hassan Vosoghinia[13], Farnood Rajabzadeh[14], Alireza Bary[15], Massih Bahar[16], Ali Javadmanesh[17,18], Jamshid Sorouri-Khorashad[19], Mohammad Hassan Emami[7], Nasser Ebrahimi Daryani[10], Hans F.A. Vasen[20], Ladan Goshayeshi[1,13*] and Hesam Dehghani[2,21*]

Crc with revised Bethesda criteria :



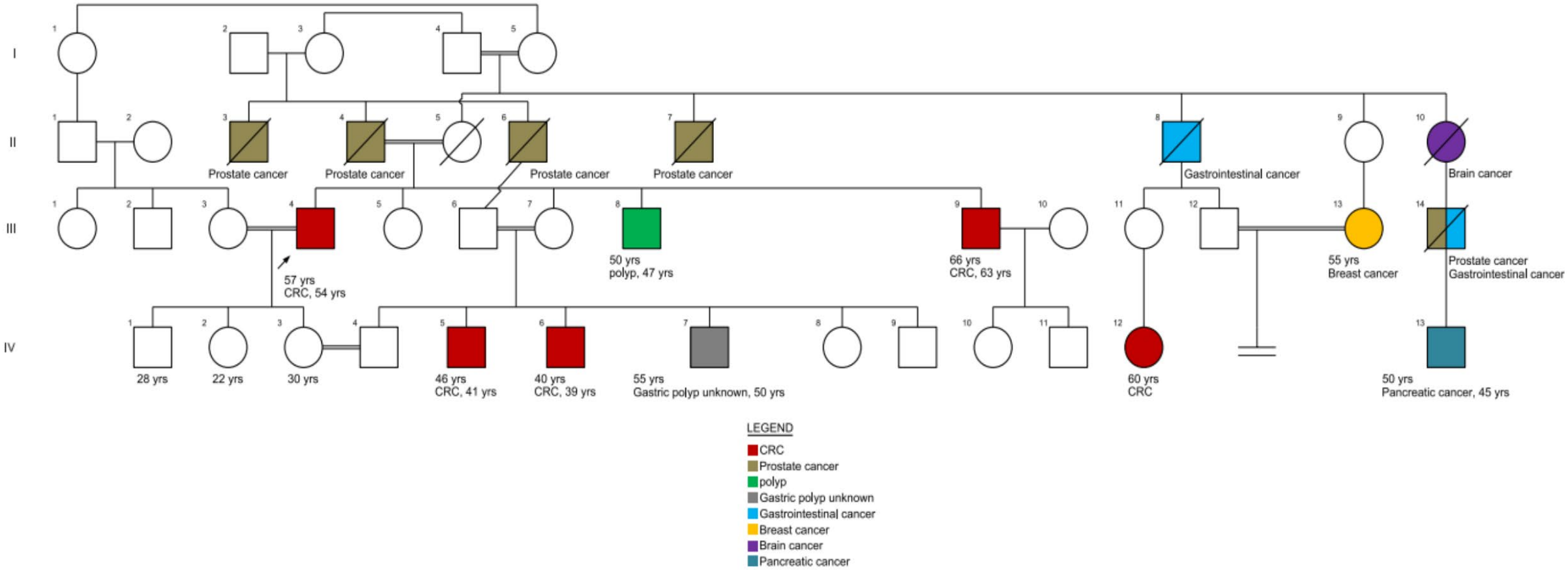
syndrome with MLH1 mutation

58-y male with dMMR CRC

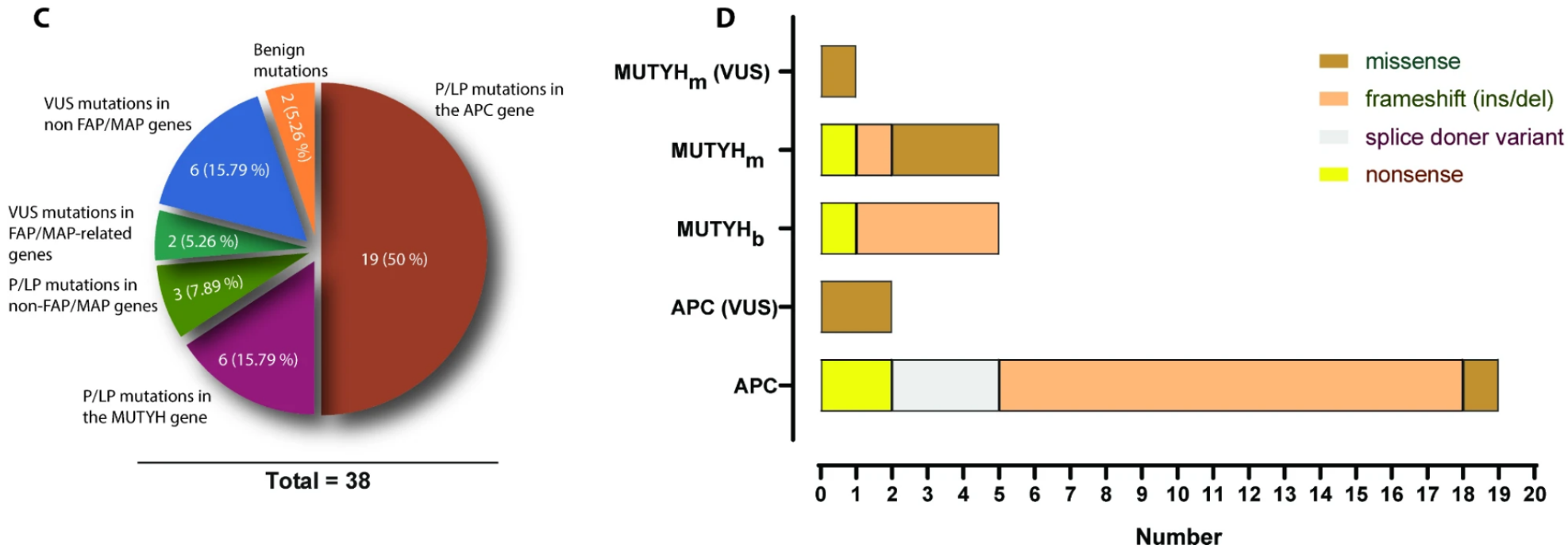


h syndrome with MSH2 mutation:

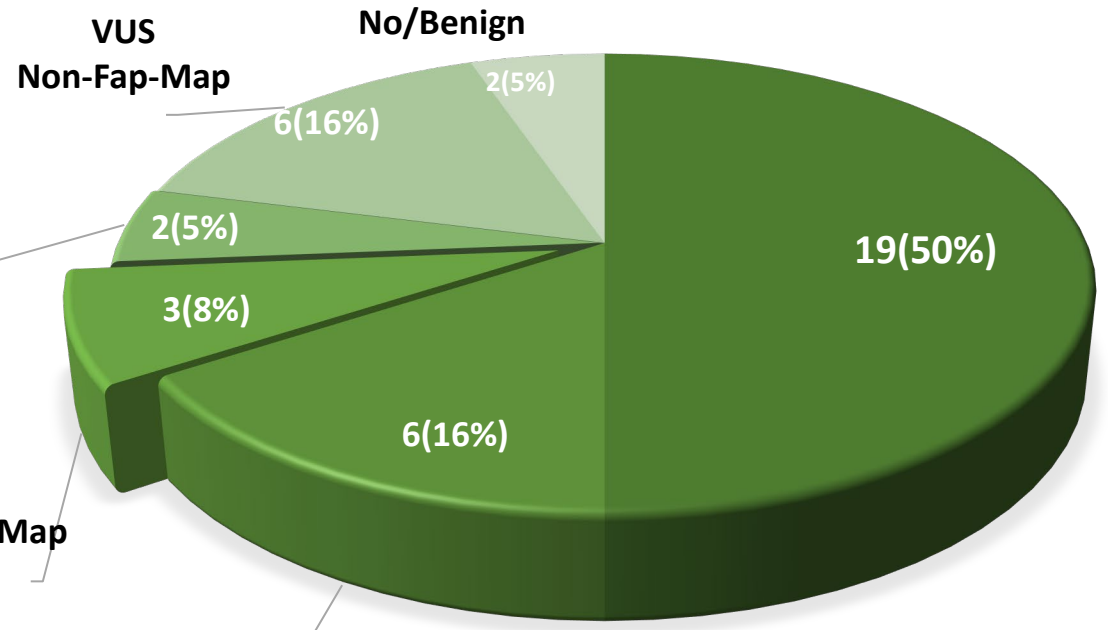
57-y male with dMMR synchronous CRC in the ascending colon



Colon polyposis >10



Colon polyposis syndromes



High Penetrance

low Penetrance →

- BRCA2(2)
- PTEN
- BLM(*bialleic*)
- RAD50

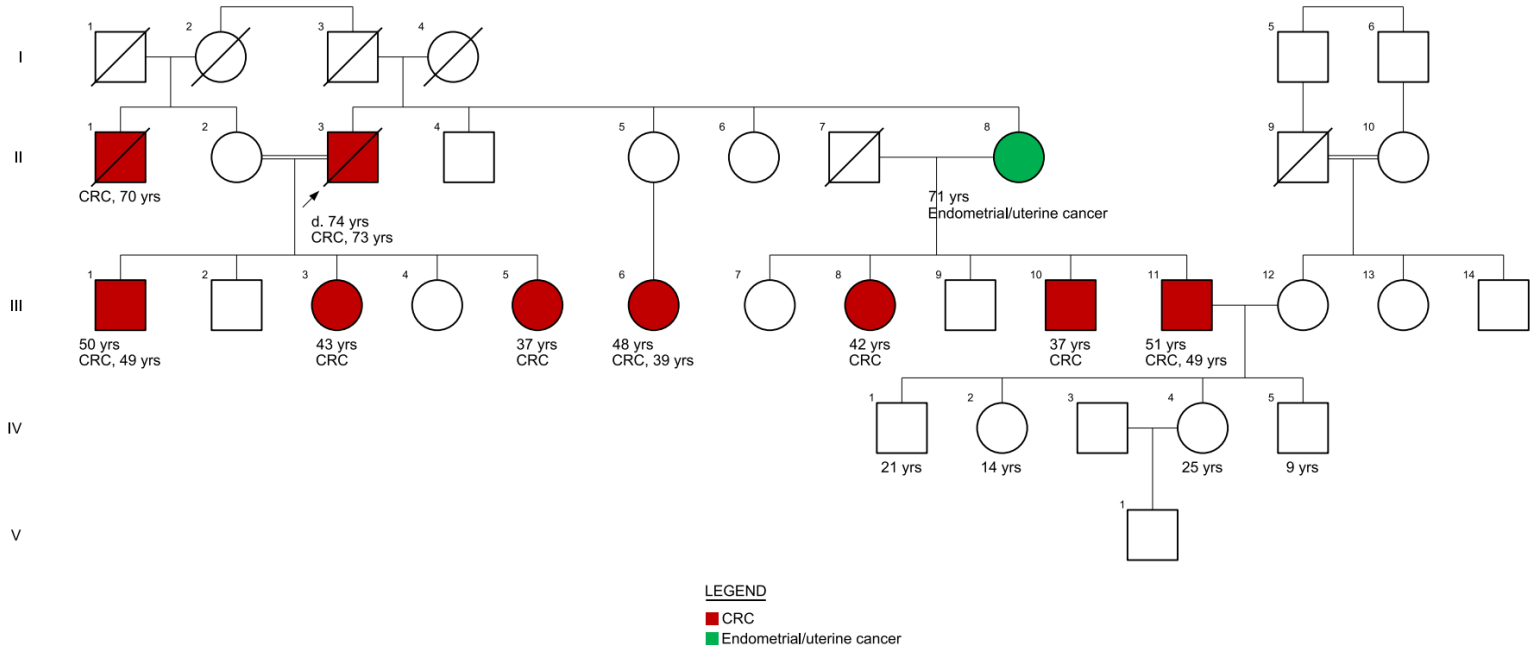
Over 100 polyps: 33%
CRC (33%)
Mean age at crc diagnosis:37.5 y

P/LP
APC

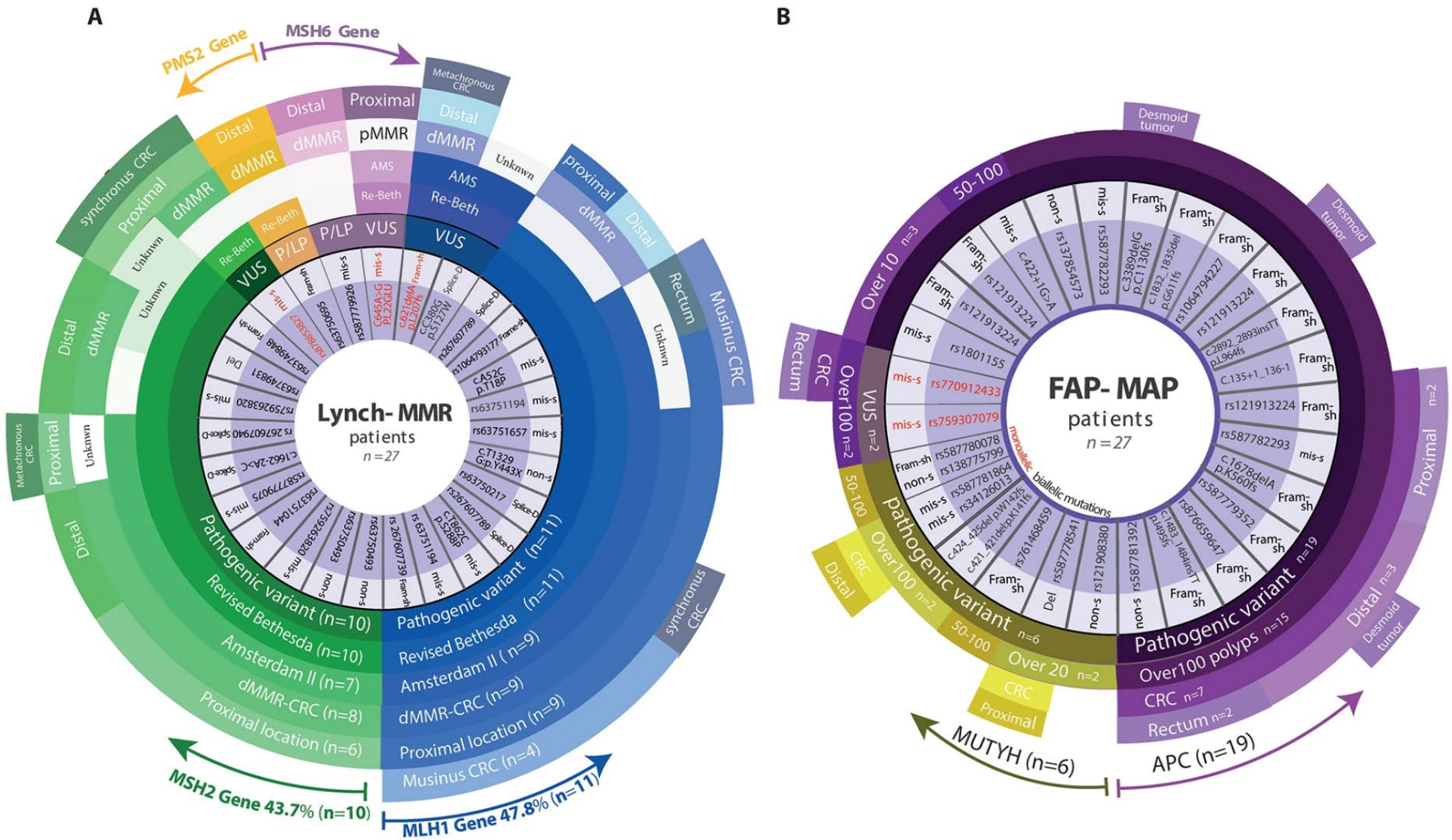
Over 100 polyps: 73%
CRC (31%)
Mean age at crc diagnosis:45.8y

family with APC mutation

74-y male with colon polyposis and CRC



From: [Germline variants in patients from the Iranian hereditary colorectal cancer registry]



Implications of identification of families with hereditary CRC

- **surveillance and prophylactic interventions, can lead to better outcomes in affected individuals especially young adults in these families .**



Cascade testing

Lynch syndrome:

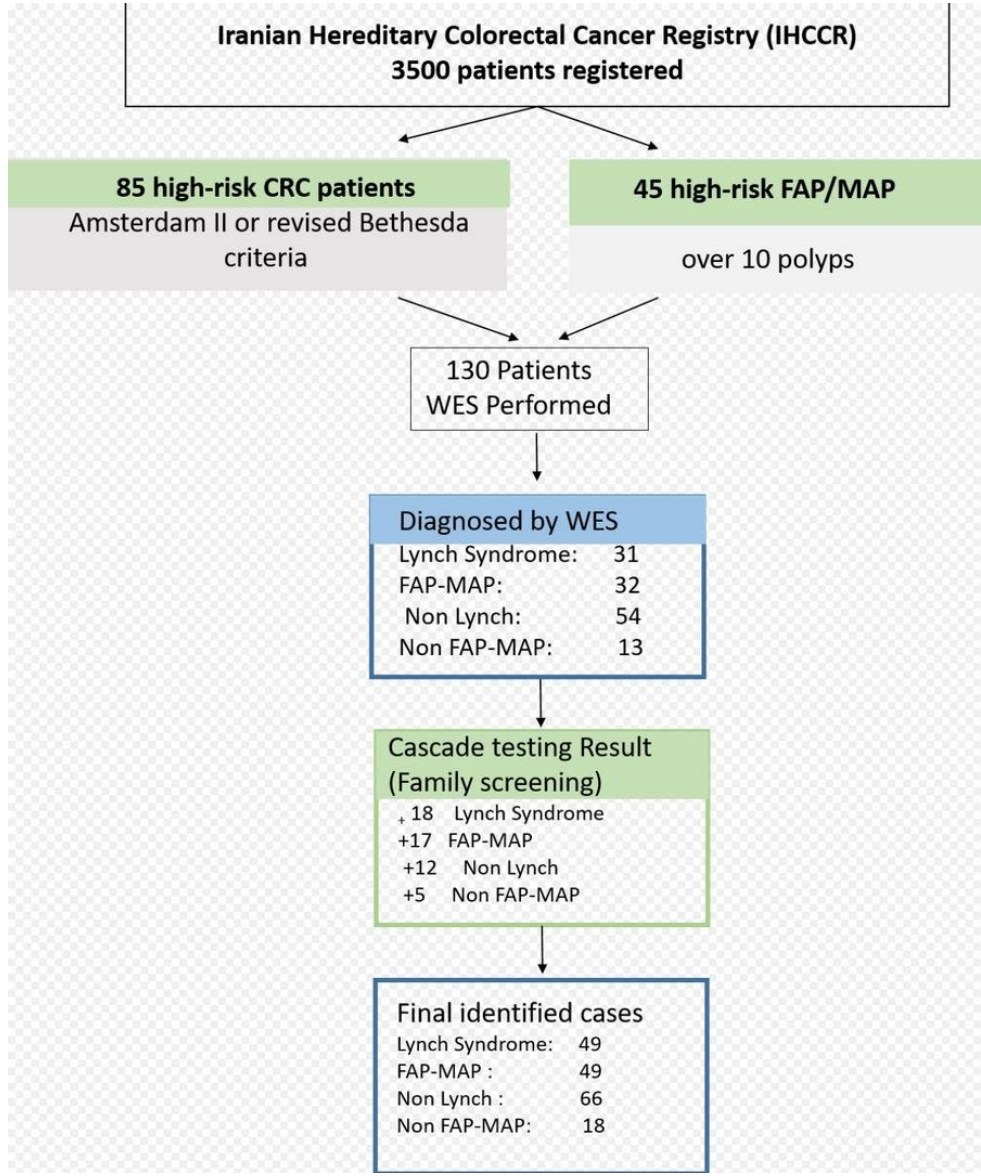
63 Cases FDR ,30 (46%) carrier of pathogenic germline mutation .

Polyposis :

35 FDR tested .18(53%) carrier of pathogenic germline mutation.

Total :98 FDR tested ,48 new case found.

	ID	Number of patient	Carrier	No Carrier	GENE	Clinvar	RefSeq	Amino Acid & Nucleic Acid Alteration	ID SNP	Zygosity
1	L6	8	3	5	MLH1	Pathogenic	NM_000249.3	c.793C>T (p.Arg265Cys)	rs63751194	Het
2	L33	2	2	-	MLH1	pathogenic	NM_000249	c.790+1G>A	rs267607789	Het
3	L27	3	2	1	MLH1	Uncertain Significance	NM_000249	c.C1103G (p.S368W)	-	Het
4	SARV	4	1	3	MSH2	pathogenic	NM_000251	c.1076+1G>T	rs267607940	Het
5	L32	5	1	4	MSH2	likely pathogenic	NM_000251	c.1662-2A>C	-	Het
6	L8	2	0	2	MSH2	Pathogenic	NM_000251	c.1835C>G (p.Ser612Ter)	rs63750493	Het
7	L56	5	2	3	MSH6	Uncertain Significance	NM-000179	c.64A>G (p.Lys22Glu)	rs1060502897	Het
8	L13	2	1	1	MLH3	Likely Pathogenic	NM_001040108	c.C3367T (p.Q1123X)	rs151133595	Het
9	L50	5	4	1	TP53	Pathogenic	NM_000546	c.G1010A (p.R337H)	rs121912664	Het
			1	0	APC	Uncertain Significance	NM_000038	c.C7477A (p.L2493I)	-	Het
10	L17	1	1	-	PMS1	likely pathogenic	NM_000534	c.C829T (p.R277X)	rs768246348	Het
11	L7	2	-	2	RB1	Uncertain Significance	NM_000321	c.T688C (p.S230P)	-	Het
12	L21	3	2	1	FH	pathogenic	NM_000143	c.G557A (p.S186N)	rs587782618	Het


Iranian Hereditary Colorectal Cancer Registry (IHCCR)
3500 patients registered
85 high-risk CRC patients
Amsterdam II or revised Bethesda criteria
45 high-risk FAP/MAP
over 10 polyps
130 Patients
WES Performed
Diagnosed by WES
Lynch Syndrome: 31
FAP-MAP: 32
Non Lynch: 54
Non FAP-MAP: 13
Cascade testing Result (Family screening)
+18 Lynch Syndrome
+17 FAP-MAP
+12 Non Lynch
+5 Non FAP-MAP
Final identified cases
Lynch Syndrome: 49
FAP-MAP : 49
Non Lynch : 66
Non FAP-MAP: 18

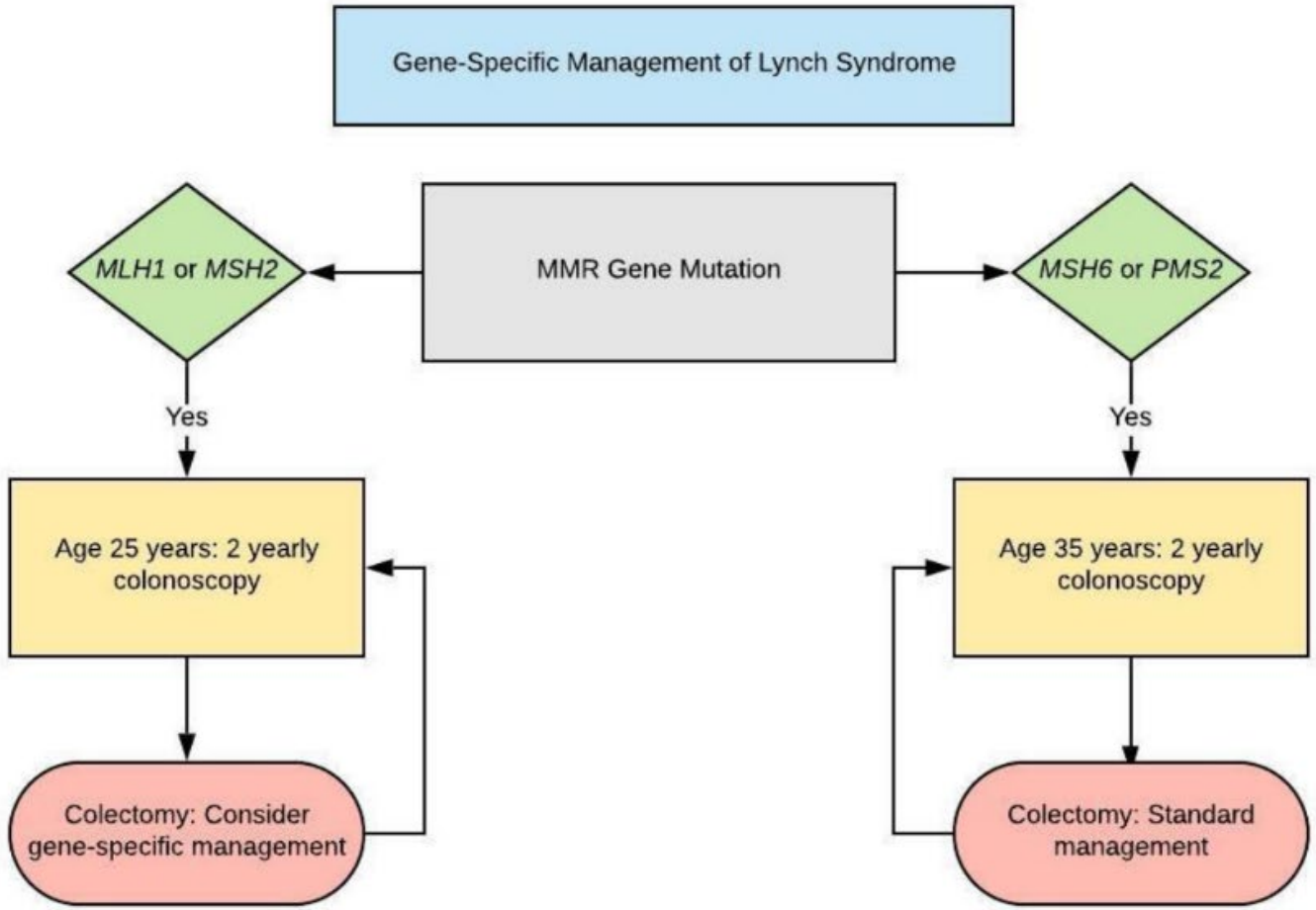


Figure 2 Gene-specific management of Lynch syndrome. MMR, mismatch repair.

Surveillance for lynch syndrome

35y :

endoscopy every 2 years

U/A yearly ,

endometrial sampling yearly

We recommend screening for Helicobacter pylori in patients with LS and eradication therapy.

FAP and colectomy:

- polyps >10mm in diameter,
- high grade dysplasia within polyps
- significant increase in polyp burden between screening examinations.

Surveillance in FAP:

colonoscopy at age 12–14 years every 1–3 years.

upper GI starting at age 25 years.

Annual thyroid ultrasound starting in the late teens.

Desmoid tumors: Regular imaging (CT/MRI) post-surgery.

Prevention and lifestyle modification in familial CRC:

► We suggest that individuals at increased familial risk of CRC should be strongly encouraged

- **not to smoke,**
- **to maintain a normal body mass index (BMI),**
- **to moderate their consumption of red and processed meat,**
- **and to exercise regularly.**

DISEASES OF THE COLON & RECTUM VOLUME 67: 2 (2024)

راهنمای بالینی تشخیص، پیگیری و مدیریت سرطان کولورکتال ارثی در بیماران و خانواده های در معرض خطر: رویکردی جامع بر پایه شواهد ژنتیکی در ایران

1- تعریف اهداف و محدوده گایدلاین

هدف از تدوین این گایدلاین، فراهم کردن راهنمایی های بالینی برای شناسایی، ارزیابی و مدیریت بیماران مبتلا به سرطان کولورکتال ارثی در ایران است. این گایدلاین به طور خاص بر تشخیص و بررسی جهش های ژنتیکی مرتبط با سندرم های کولورکتال پلیپوز و غیرپلیپوز تمرکز دارد و با توجه به نتایج مطالعه ی توالی یابی کل اگزوم (WES) بر روی بیماران ایرانی، پیشنهاداتی را برای بهبود غربالگری و مشاوره ژنتیکی ارائه می دهد. این راهنما توصیه می کند که انجام تست های ژنتیکی برای بیماران با بیش از ۱۰ پلیپ و همچنین افرادی با سابقه خانوادگی سرطان روده بزرگ و سایر سرطان ها مورد توجه قرار گیرد، زیرا در بیماران دارای سندرم پلیپوز، ۵۰٪ از جهش ها در ژن APC و ۱۵.۷۹٪ در

Collaboration Opportunity

- We are open to national and international collaboration on hereditary CRC research

- Seeking multicenter studies to improve early detection and prevention.

Contact

- Dr ladan goshayeshi: director of IHRCC registry
- dr.ladan_goshayeshi

Dr lena goshayeshi : manager of IHRCC registry

dr_lena_goshayeshi

Thank you for your attention.



