Thanks

Hadassah Medical Center

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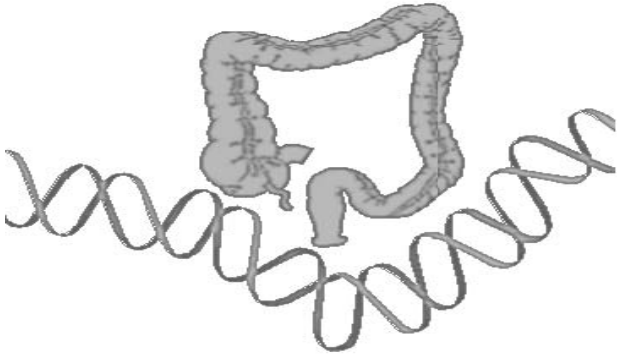

TASMC

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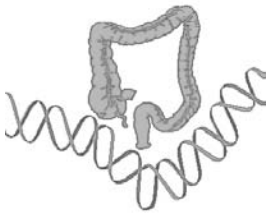
ICA

LS Diagnosis in Israel



Goals of this presentation:

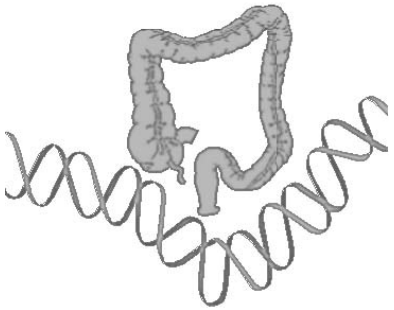
1. Introduce the extent of Lynch syndrome in Israel

2. Provide data about the genetic and clinical heterogeneity of LS in Israel

3. Show the unique features of LS in the Israeli & the Jewish populations

4. Show why LS work-up requires collaboration of multidisciplinary expert teams

Genetic Aspects of Lynch Syndrome (HNPCC) in the Israeli population



2004-2012

Integrative data

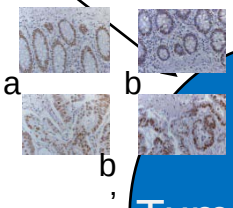
Hadassah, Rabin, TASMC

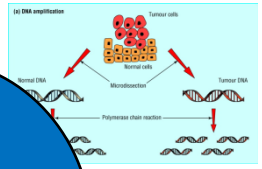
LS - Diagnostic Algorithm

Clinical criteria
(Amsterdam, Bethesda)

Other

Mutation testing
(Familial; Founder)





Tumor testing
IHC
MSI

Positive

Negative

Gene testing

sequencing

MLPA

MLH1

HNPCC unlikely

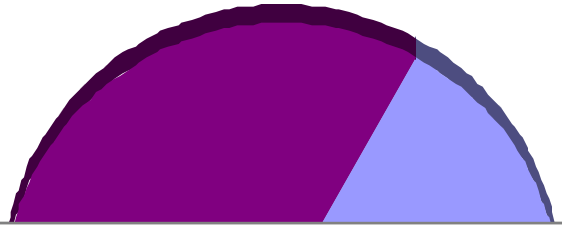
Negative

BRAF/Methylation

141 LS Families

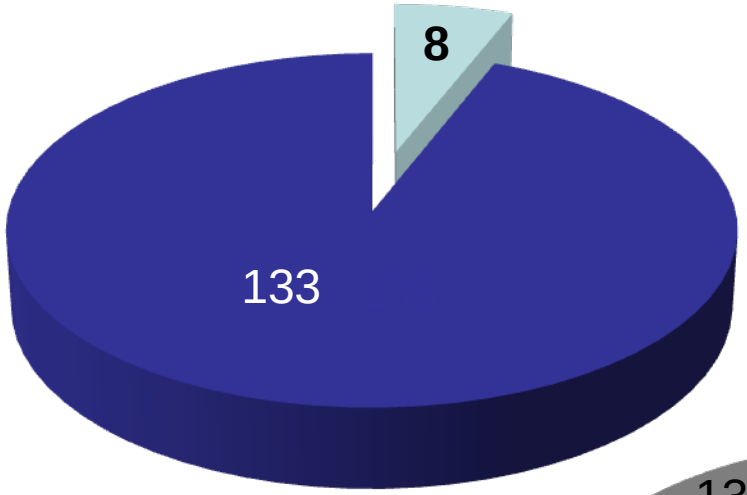
81 (58%) mutation carriers

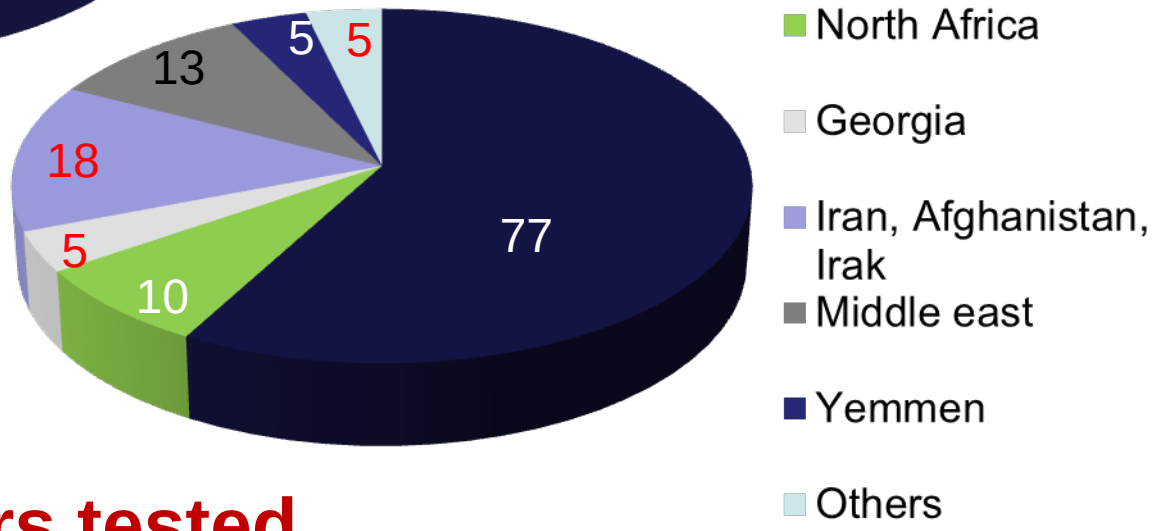
60(42%) Positive tumor testing with no mutation



Positive Tumor testing
and/or
Disease causing mutation

141 LS Families - Ethnicity

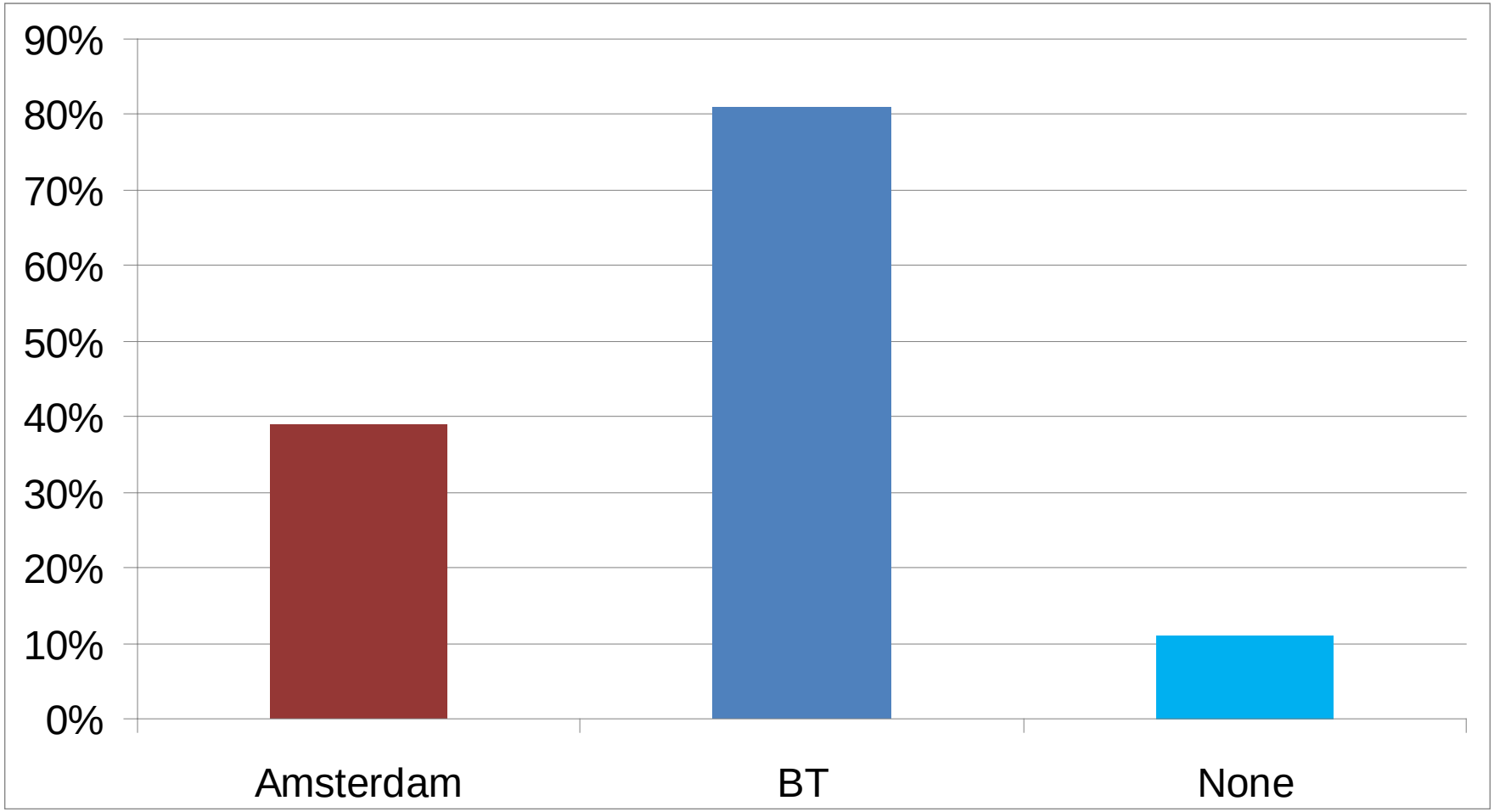




303 family members tested
234 (77%) are carriers

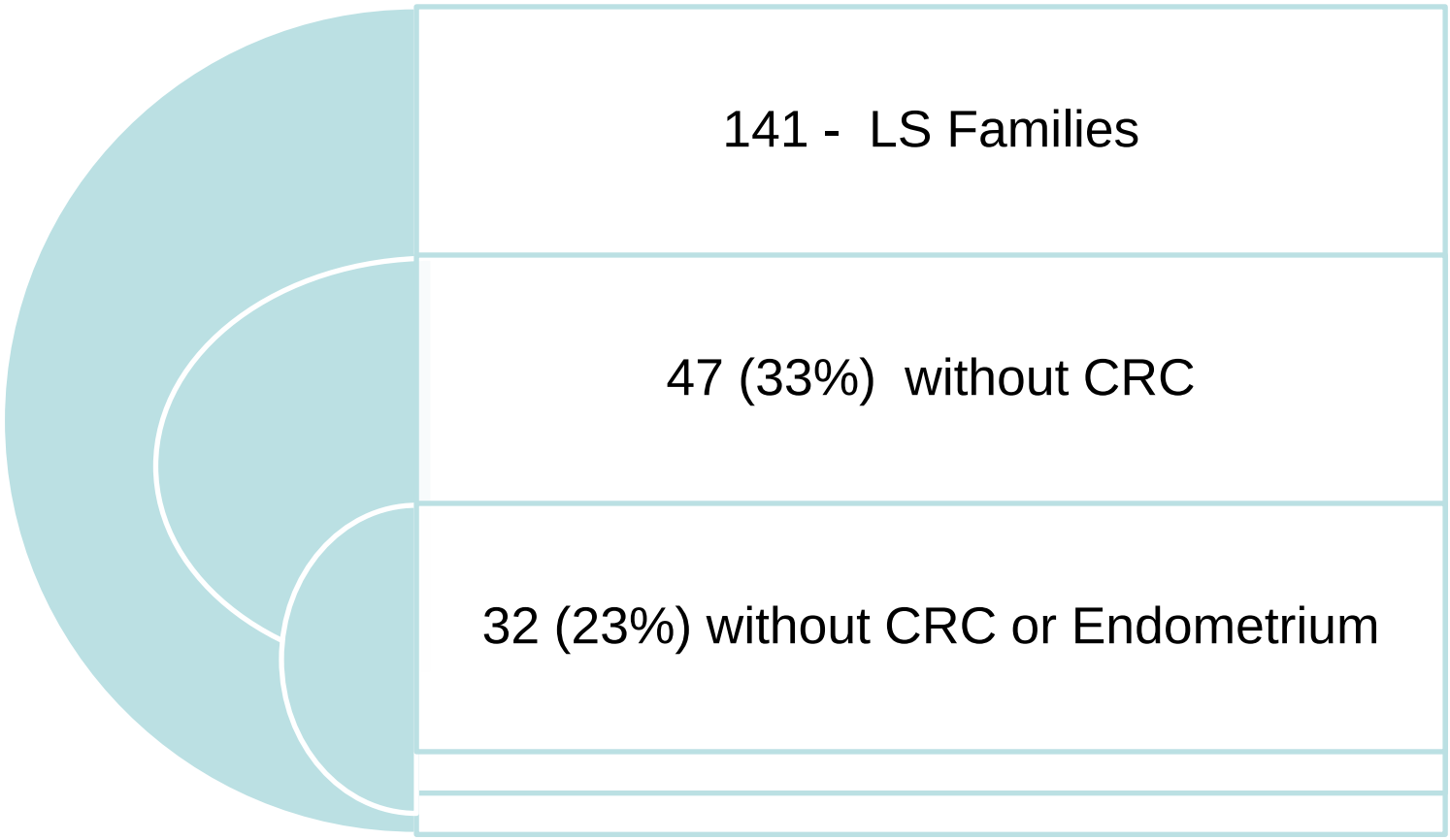
141 LS Families

Clinical criteria

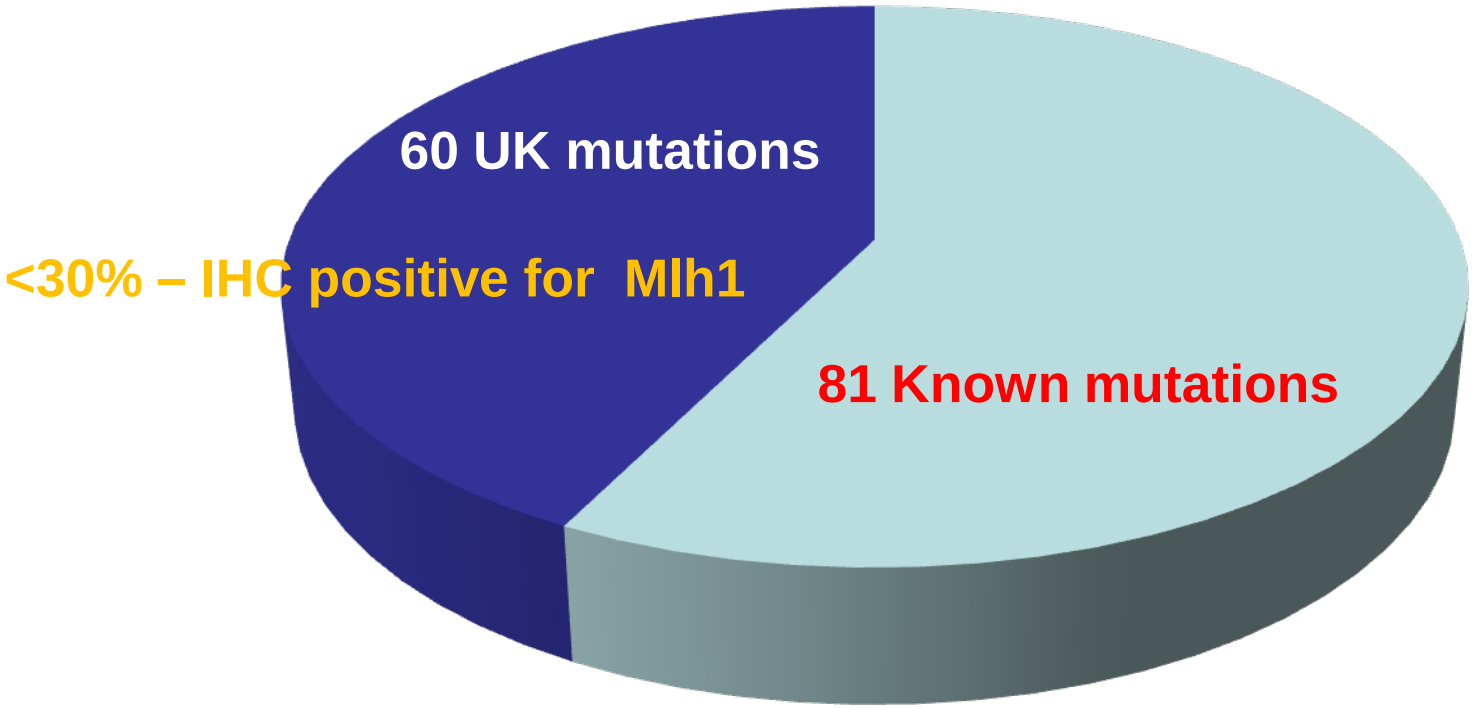


141 LS Families

Phenotype

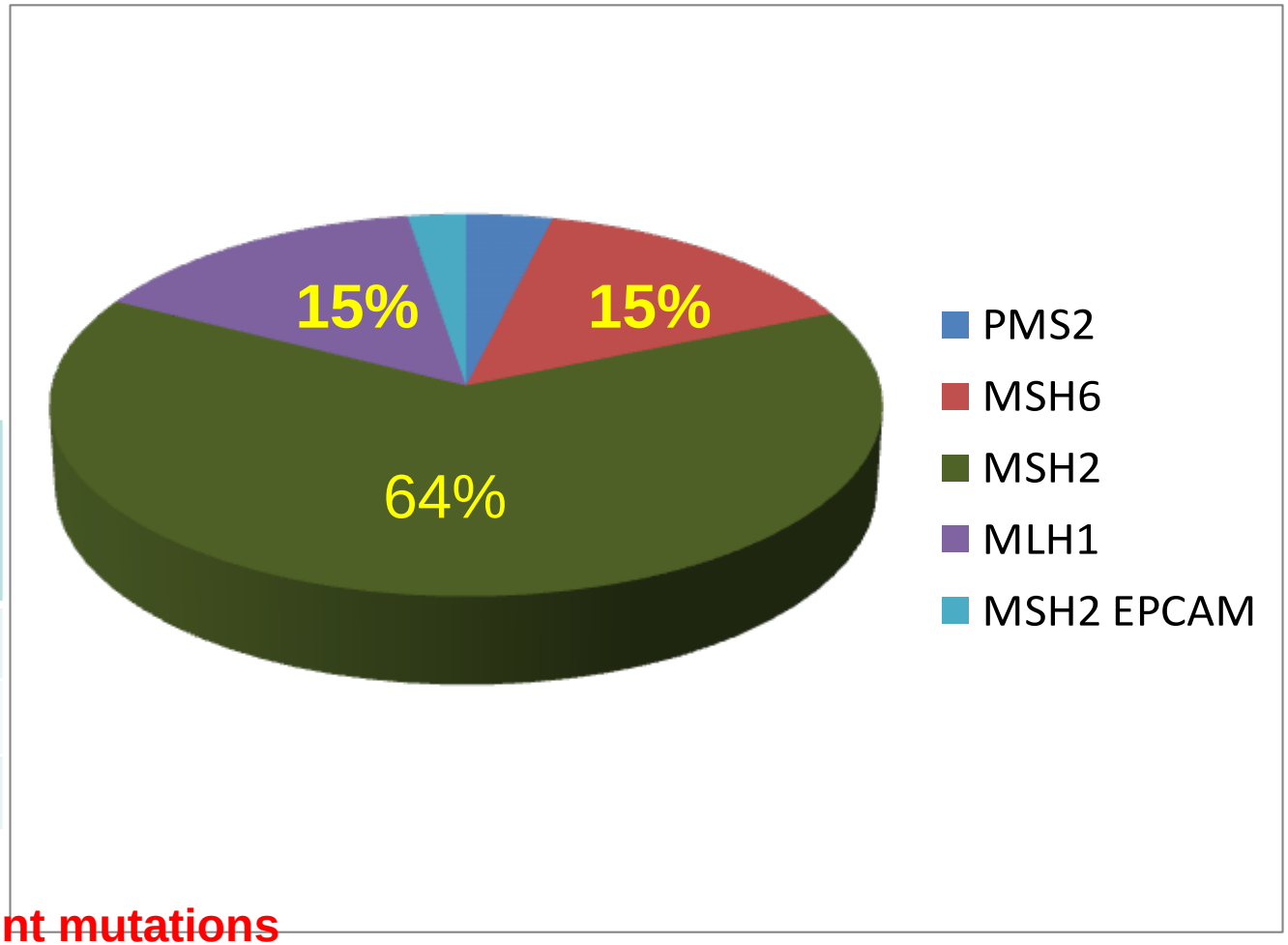


Mutations identified in 81/141 (57%) Families



Spectrum of Mutations

Mutation number	Number of families
35	1 family
3	2 families
4	founder



Iranian Jews – 3 different mutations

Spectrum of Mutations

Gene	Mutations	Splice mutations	Big Deletion	Amsterdam	BT	None
MSH2	52 (64%)	4	4 (10%)	25 (48%)	48 (82.7%)	5
MLH1	12 (15%)	4	1 (0.8%)	7 (58%)	10 (83%)	2
MSH6	12 (15%)	0	0	1 (8%)	9 (75%)	1
PMS2	3 (4%)	0	0	2 (66.6%)	3 (100%)	
MSH2 EPCAM	2 (2%)	2	2 (100%)	2 (100%)	2 (100%)	
	81 (100%)	10/81 (12%)	7/81 (9%)			

* 2 mutations (MLH1, MSH2) are classified as variants of unknown significance

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	81 (100%)	10/81 (12%)	**7/81 (9%)**			

*** 2 mutations (MLH1, MSH2) are classified as variants of unknown significance**

Founder mutations

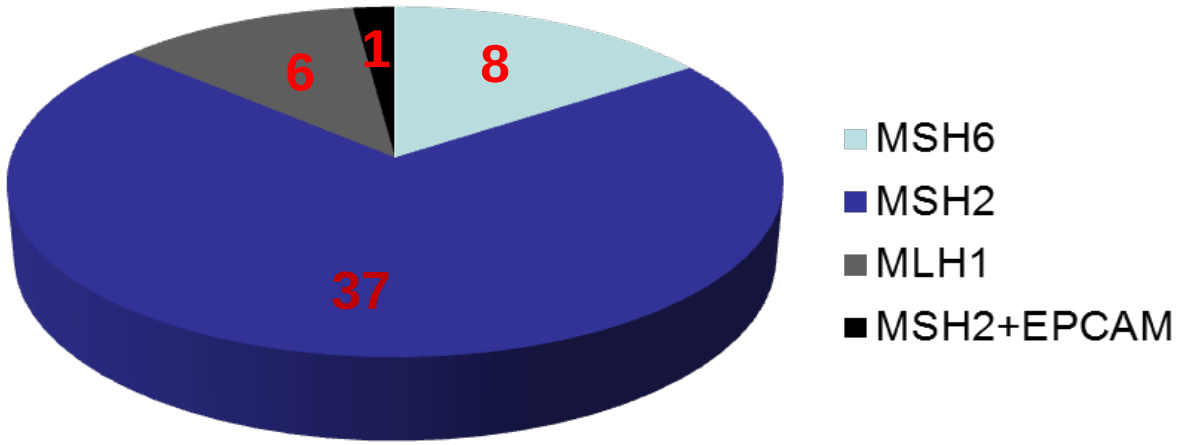
Gene	Mutation	Number families	Ethnicity	Amsterdam	BT
MSH2	c.970-971delCA	5	5 Georgian	3	2
MLH1	c.1770-1771delAG	2	Afghanistan	2	0
MSH2	del exons 9-10	1 +	Ethiopia	0	1
MSH2	1906G>C	27	Ash	10	17
MSH6	c.3984_3987dupGTCA	6	Ash	0	4
MSH6	c.3959_3962delCAAG	2	Ash	0	1

Ashkenazi, Georgian, Afghan, Ethiopia

LS Ashkenazi families

LS was diagnosed among 77 Ashkenazi families.

Mutations detected in 52/77 (67%)



3 founder mutations in Ashkenazi

2002 - A founder mutation in MSH2 (c.1906G>C)

- 0.6% of CRC
- 0.04-0.06% in the general population
- 18-33% of Amsterdam Criteria positive cases
- Highly penetrant.

2009 – A founder mutation in MSH6 c.3984_3987dupGTCA

- 0.3% of CRC 0.6% Endometrial Cancer
- 0.03% in the general population
- Tumors tend to occur later in life –late penetrance

2010 – A founder mutation in MSH6 - c.3959_3962delCAAG

- Tumors tend to occur later in life – low/late penetrance
- 0.1% of CRC 0.6% Endometrial Cancer
- Tumors tend to occur later in life –late penetrance

LS Ashkenazi families

The 3 founder mutations detected in 35/ 77 (45%) LS positive families

The 3 founder mutations detected in 35/52 (67%) mutation positive families

c.1906G>C (35%)

c.3984_3987dupGTCA (7%)

c.3959_3962delCAAG (3%)

* Bias!

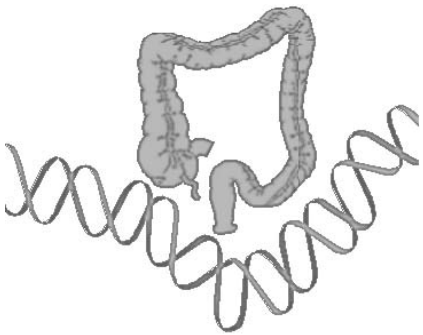
LS in Ashkenazi families – unique approach

HBOC

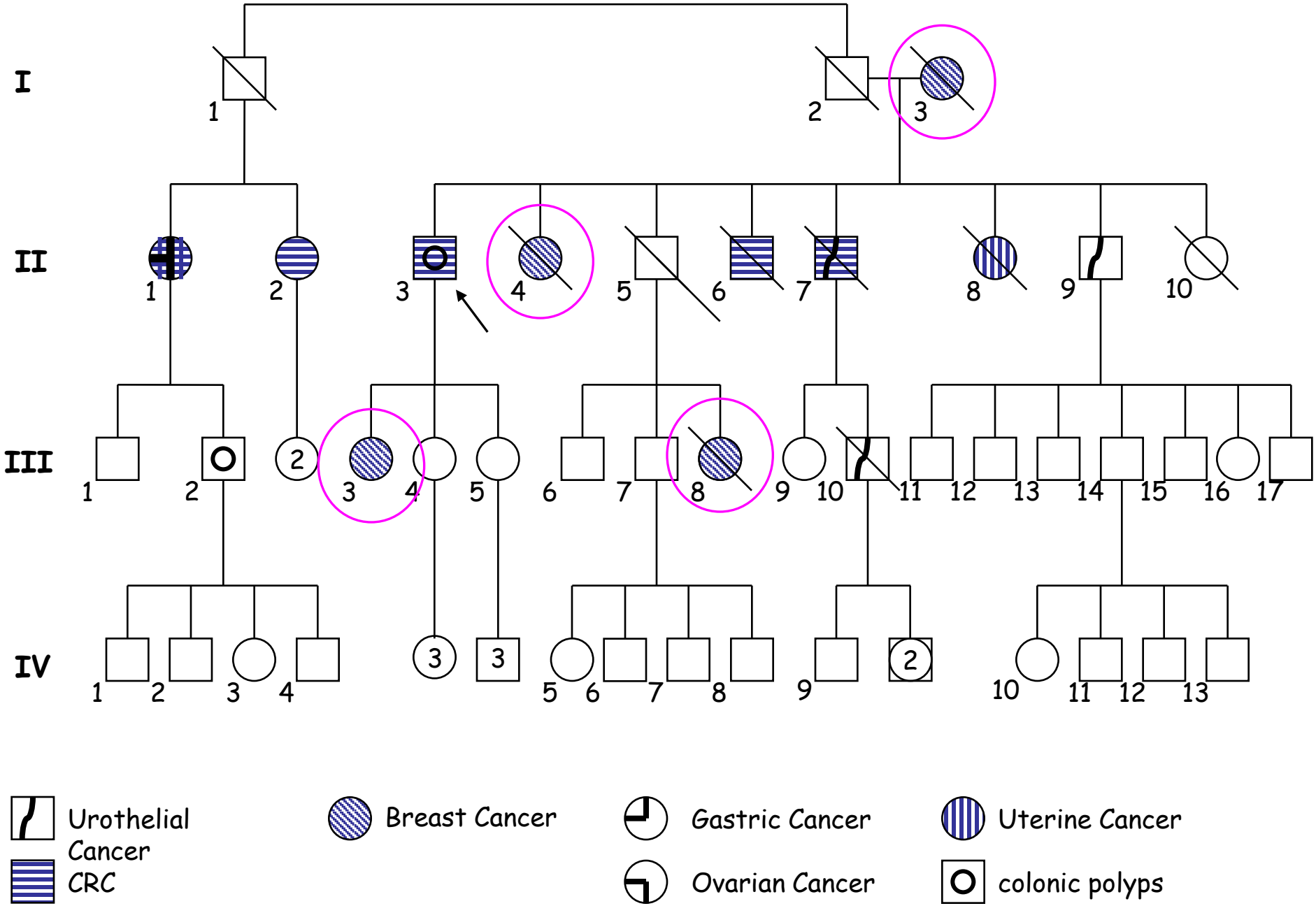
Hereditary Breast Ovarian Cancer

MMRD

Constitutional Mismatch Repair Deficiency



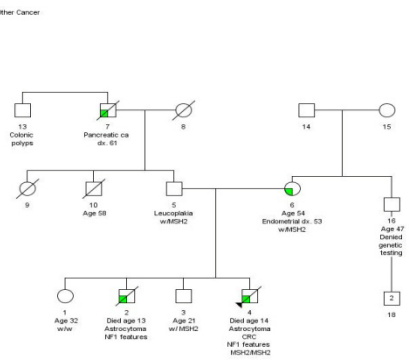
MSH6 c.3984-3987dup Ashkenazi Mutation



C-MMRD
(Autosomal recessive LS)

- Prevalence higher among consanguineous populations
- Prevalence higher among ethnic groups with founder mutations
- Deserves special genetic counseling (spouse testing; Prenatal diagnosis)

C-MMRD in Israel



3 MMRD Families

III

1 Muslim (consanguineous) - PMS2 - Biallelic for c.686_687delCT

II

2 Ashkenazi:
MSH2 - Biallelic for c.1906G>C
MSH6 - Biallelic for c.3984_3987dupGTCA/c.3959_3962delCAAG

I

Familial Cancer (2009) 8:187–194
DOI 10.1007/s10689-008-9227-3

Homozygosity of *MSH2* c.1906G→C germline mutation is associated with childhood colon cancer, astrocytoma and signs of Neurofibromatosis type I

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LS Diagnosis in Israel - Summary

A genetic heterogeneous condition

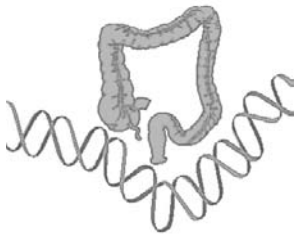
5 Genes (EPCAM, MSH2, MLH1, MSH6, PMS2)

Over 50 private mutations
(splice mutations, deletions)

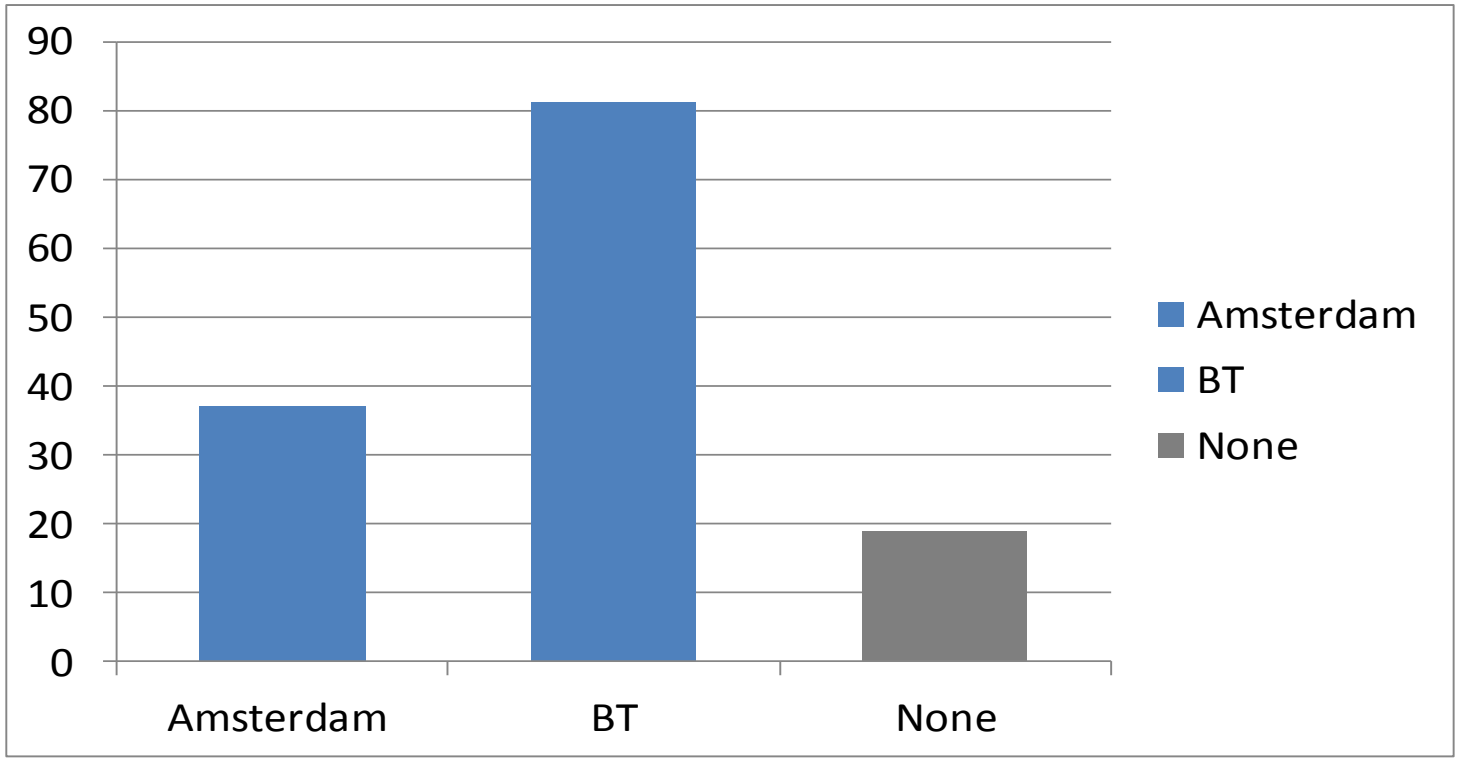
Founder mutations

Reliable diagnosis
(DM vs UV; sporadic MSI; Inherited methylation)

Other syndromes



1906G>C Ashkenazi Mutation Genotype -Phenotype



10/27 (37%) AC
22/27 (81%) BT
5 (18%) – no clinical criteria

37/55 (67%) AC positive
67/114 (59%) BT positive

As mentioned before, having AC does not necessarily mean LS. Testing was positive in 70%. Dr. Kariv will speak more about the other 30%. Note that the % of LS among BT positive families is quite high in our cohort.