Familial Colorectal Cancer Type X in Israel- are we different?

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Familial Colorectal Cancer Type X (FCCTX)

- Families who fulfill the Amsterdam criteria but that are mismatch repair (MMR) proficient
- About 60% of broad Amsterdam positive families in Israel
  (Goldberg et al., Fam Cancer 2008)
- Worldwide about 40-50%
  (Wijnen et al NEJM 1998)

Amsterdam Criteria

(1) 3 cases of CRC, in which 2 of
the affected individuals are first-degree relatives of the third;
(2) CRCs that occur in 2 generations;
(3) 1 CRC diagnosed before the age of 50 years;
(4) familial adenomatous polyposis not diagnosed in the family

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Online article and related content current as of February 5, 2009.

Lower Cancer Incidence in Amsterdam-I Criteria Families Without Mismatch Repair Deficiency: Familial Colorectal Cancer Type X

Noralane M. Lindor; Kari Rabe; Gloria M. Petersen; et al.

JAMA. 2005;293(16):1979-1985 (doi:10.1001/jama.293.16.1979)

GASTROENTEROLOGY 2006;130:1995–2000

Prospective Results of Surveillance Colonoscopy in Dominant Familial Colorectal Cancer With and Without Lynch Syndrome

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161 Amsterdam positive families

90 MMR-

71 MMR+

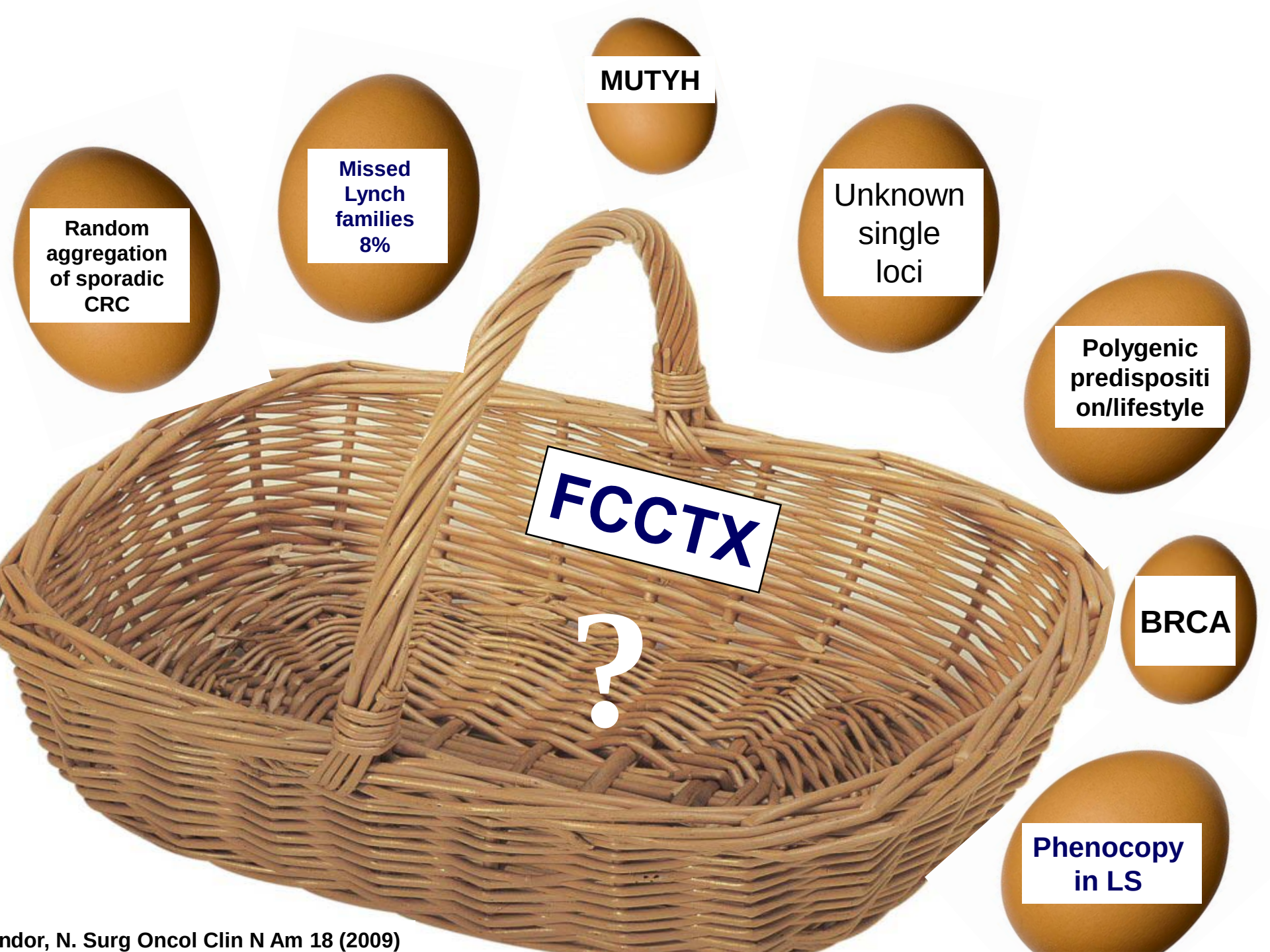
The incidence for colonic and extracolonic cancers in FCCTX families was significantly lower than in Lynch families

Lindor N, Surg Clin N Am, 2009

	Lynch Families	Type X Families	Comparison between the Lynch and Type X Families
Bisgaard et al[7]	27	12 plus 46 other HNPCC-like	Mutation-negative group less likely to have more than 1 CRC; first cancer more likely to be rectal, less likely to have HNPCC-associated extracolonic tumors; and mean age at diagnosis of first cancer 6 years older
Renkonen et al[11]	11	15[b]	No evidence of MMR gene mutations being missed in type X group, using RNA expression assay
Schiemann et al[12]	NA	19	Type X tumors more likely to be in distal colorectum; 9 years older at diagnosis than MSI-high families
Valle et al[17]	26	38	Type X families 12 years older at diagnosis and CRC more likely to be distal, not mucinous, and probands less likely to have multiple primary tumors
Lindor et al[9]	90	71	Type X had older age and lower risk of diagnosis of CRC; no increased risk for non-CRC tumors
Mueller-Koch et al[15]	25	16	Type X families 11 years older at diagnosis of CRC; only 14% tumors were proximal; fewer synchronous, metachronous, and extracolonic tumors; higher colorectal adenoma to carcinoma ratio suggesting slower progression from precancer to cancer.
Dove-Edwin[16]	26	45[a]	Groups equally likely to develop high-risk adenomas during follow-up, but interval cancers arose only in the Lynch Group. Concluded that surveillance interval can be lengthened in type X
Llor et al[18]	10	15[c]	Type X had more left-sided tumors without tumor-infiltrating lymphocytes; 6 years older at diagnosis; fewer family members with CRC or endometrial cancer

Lindor N, Surg Oncol. Clin N Am, 2009

	Lynch Syndrome	FCCTX
Colorectal		
Cancer risk	Very high	Modestly increased
Age of onset	~45 y average	50s–60s
Usual location	Proximal colon	Distal colon
Polyps	Few	More
Malignant transformation	Rapid	Less rapid
Other cancers		
Endometrial risk	Very high risk	Risk not significantly increased
Other cancer sites	Many others	None known
Germline MMR genes	Mutations found	No mutations found
CRC tumor testing	Microsatellite instability	No microsatellite instability (by definition)
CRC tumor staining	Loss of MMR protein expression	Normal expression



ndor, N. Surg Oncol Clin N Am 18 (2009)

Molecular profiling

	Type X, *N* = 18 Tumors (%)	Lynch, *N* = 31 Tumors (%)	Sporadic from Literature (%)	*P*-value for Type X vs Lynch	*P*-value for Type X vs Sporadic
Nuclear β-catenin	39	81	95	0.005	0.000005
CTNNB1 mutations	0	29	6	0.007	NS
CDX2 alteration: decreased protein	11	6	16	NS	NS
KRAS exon 2 mutations	17	26	30	NS	NS
BRAF V600E	4	0	3	NS	NS
P53 protein stabilization	44	13	52	0.04	NS
TP53 mutation	26	13	52	NS	0.01
Chromosomal instability by CGH	44	Not done	79	—	0.00006

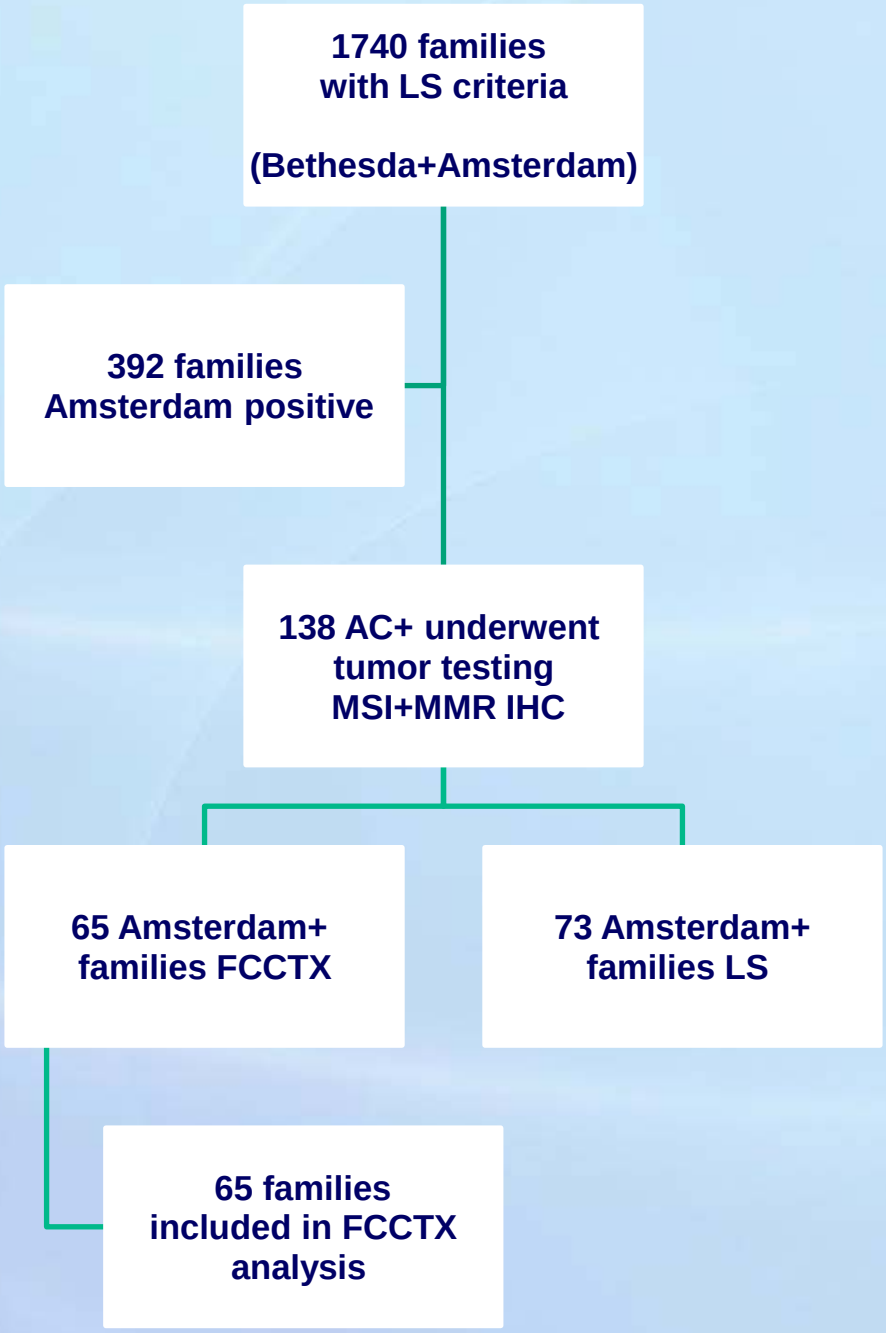
Lindor N, Surg Oncol. Clin N Am, 2009, R M, Abdel-Rahman W et al, Oncogene 2005

Unresolved Clinical Issues for FCCTX

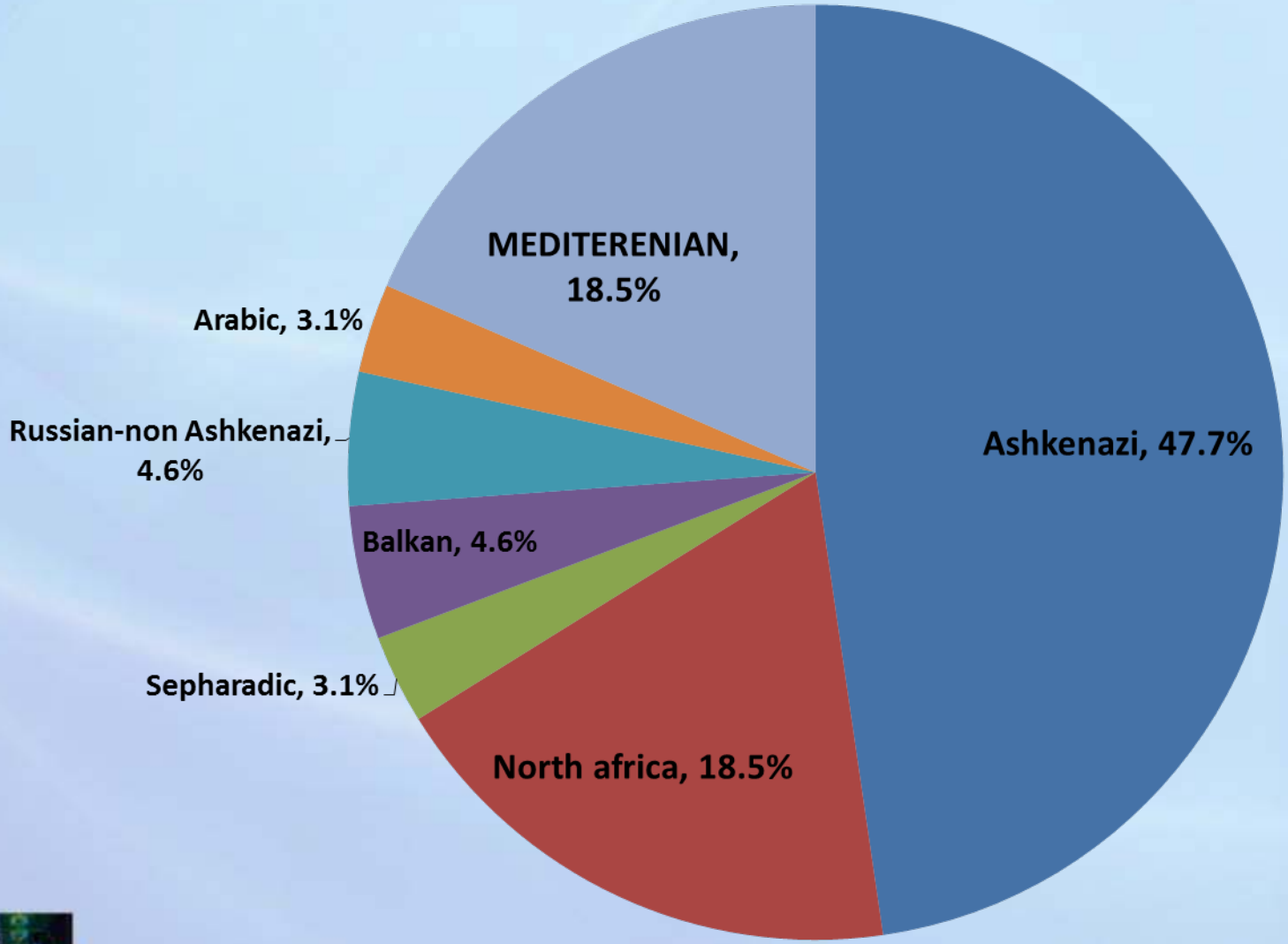
- **Colonic and Extracolonic tumor lifetime risk** - need for prophylactic surgery, PGD (Perea et al, 2009)
- **Colonic Surveillance:** intervals & age of onset
- **Extra colonic surveillance**? Yes/no, Which?
- **Algorithm for further genetic workup-** family testing and recommendations

Patients and Methods

- Hereditary CRC registry in 3 tertiary centers in Israel:
  - TASMC
  - Hadassah
  - Rabin
- Families who fulfill Amsterdam criteria and in which Lynch syndrome was ruled out by Tumor testing (MSI+MMR IHC)
- Pedigree was studied for detailed cancer history


1740 families
with LS criteria
(Bethesda+Amsterdam)
392 families
Amsterdam positive
138 AC+ underwent
tumor testing
MSI+MMR IHC
65 Amsterdam+
families FCCTX
73 Amsterdam+
families LS
65 families
included in FCCTX
analysis

Results-Ethnic Origin



Results-Cancer Morbidity (1)

- **Earliest age of cancer in family- 43.08±10.5**
- **Earliest age of cancer in proband- 50±11.1**

- **Earliest age of CRC in family- 50.54±13**
- **Earliest age of CRC in proband- 52.82±10.5**
- **Age of CRC diagnosis for the general Israeli population: 73.36±10.65**

Age for CRC Diagnosis

Group	N	Mean	Std. Deviation	Std. Error Mean
Syndrome X	34	52.9412	10.69959	1.83497
Lynch	113	47.2212	13.44216	1.26453

p-value=0.025

Results-Cancer Morbidity (2)

- 3/28 cases (10.7%) of **Interval cancer** within 5 years, but no data for 37 families

10.7% in 5 years

- **Family members with cancer 4.39±1.33**
- **Family members with CRC 2.37±1.59**
- **Family members with extracolonic cancer 2±1.6**
- **Family members with cancer ≤50Y 1.3±0.97**

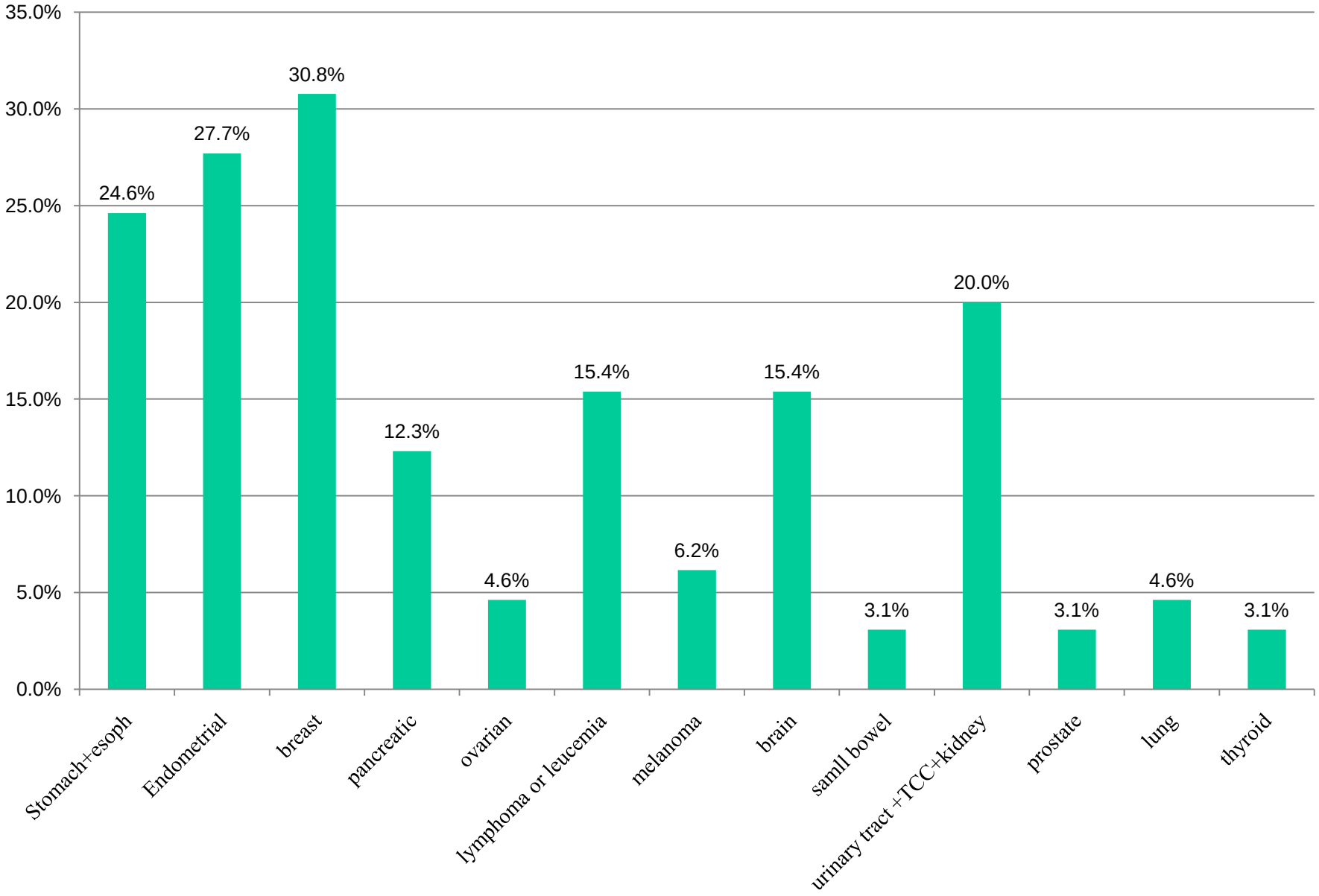
CRC and Colonic Polyps in Proband& Family

- **46/65 (70.7%) probands had CRC**
  - **15 right sides**
  - **32 left sided (1 pt with 2 CRCs)**
- **33/65(50.75%) families had polyps**
  - **19(57.6%) adenomatous**
  - **8(24.2%) hyperplastic**
  - **7(21%) unknown**
- **Polyp age of diagnosis in proband- 49.75±14.2**
- **In family- 52.7±9.6**

Extracolonic Tumors in Proband and Family

- 62/65 (95.4%) families with extracolonic cancers
- 9/43 (19.5%) **CRC probands** had extracolonic cancers
- 6.7% of CRC patients at the National CRC registry had another extracolonic cancer

Extracolonic Tumors in Proband and Family



Conclusions+Discussion

- **The Israeli FCCTX seem to be different then previously reported:**
  - **Early CRC onset**
  - **Extracolonic tumors**
  - **Higher risk for CRC then general population**
- **Cause could be more founders?**
- **Should prophylactic surgery be considered?**
- **More frequent colonic surveillance**
- **Extracolonic surveillance**
- **More aggressive further genetic workup to support future surveillance and family members testing**

Potential causes for FHCCTX: MUTYH

- Base excision repair gene
- Effect could be bi or monoallelic
- Short adenoma to carcinoma interval
- Phenotype is variable:
  - Polyposis like syndrome, or multiple adenomas and hyperplastic polyps
  - HNPCC with clinical criteria
  - early onset CRC
  - Extracolonic tumors
- Interaction with other MMR genes-MSH6

Our Cohort

- **12/65 (18.5%)North African origin, 1/12 had interval cancer**
- **33/65(50.75%) families had polyps with 19(57.6%) being adenomatous and 8(24.2%) hyperplastic**
- **<u>Should be susspected in FHCCTX families:</u>**
  - **NA origin**
  - **Consanguinity, pesodominant inheritance**
  - **Interval cancer**
  - **Presence of adenomatous or Hyperplastic polyps (serrated adenomas)**

Potential causes for FHCCTX

	APC	BRCA	PTEN	P53	MUTYH
Common Tumors	Colon, Papilla	Breast, ovary, pancreas, prostate	Thryroid, Breast, endometrium	Brain, Hematological, Breast , Sarcoma	Colon, stomach, OBGYN
Special features	Adenomatous polyps	Ashkenazi origin, OBGYN and breast	Benign hamartomatous tumors, Autoimmune diseases, Autism, Macrocephaly	Early onset Very rare	Adenomatous and hyperplatic polyps, NA origin, consangiunity
At our cohort	Very few	Significant, 13/65 tested- only 1 positive	Few fill criteria, no testing		Quite few, few tested

THANK YOU