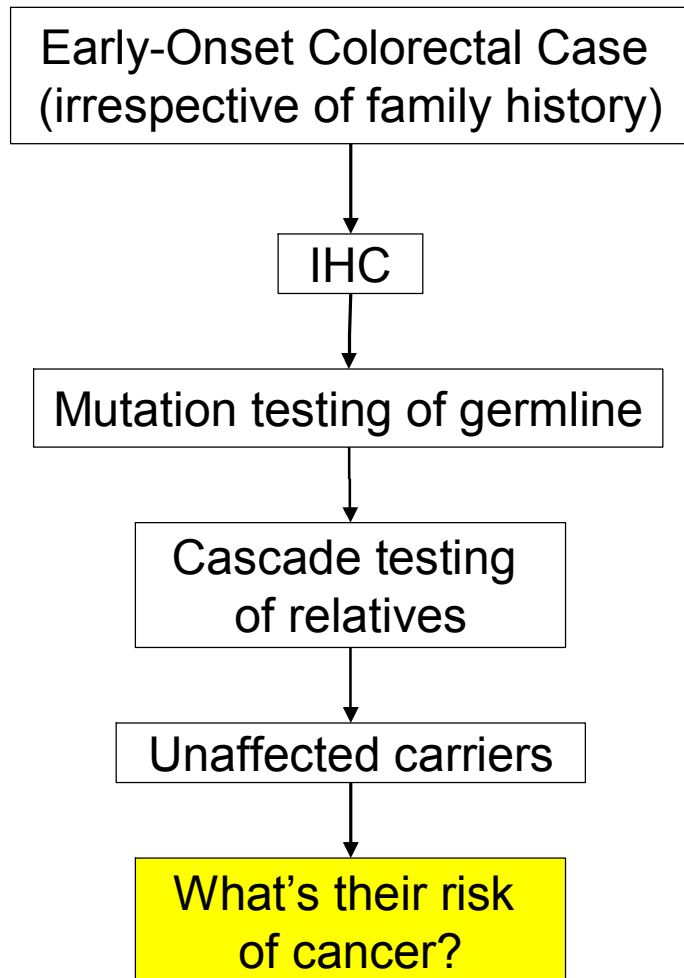


What are the real cancer risks
in Lynch syndrome (HNPCC):
a population-based study?

Mark Jenkins, University of Melbourne, Australia

Contemporary model for identification of HNPCC cases



Estimates of cumulative CRC risk to age 70.

Clinic-based
(average over six studies of
1,681 carriers)

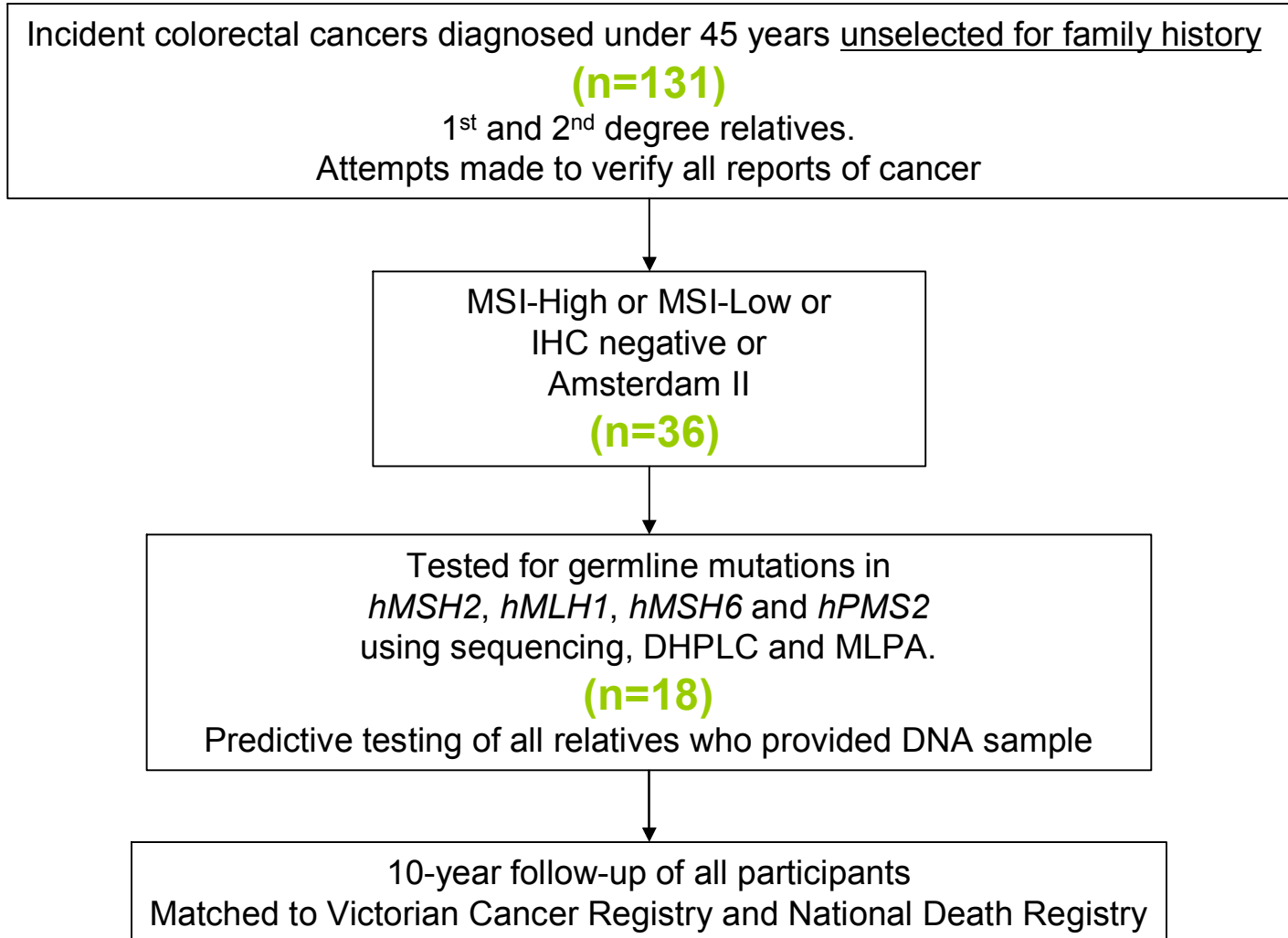
Males: 81%
Females: 63%

Population-based
(one study of 67 carriers)

Males: 74%
Females: 30%

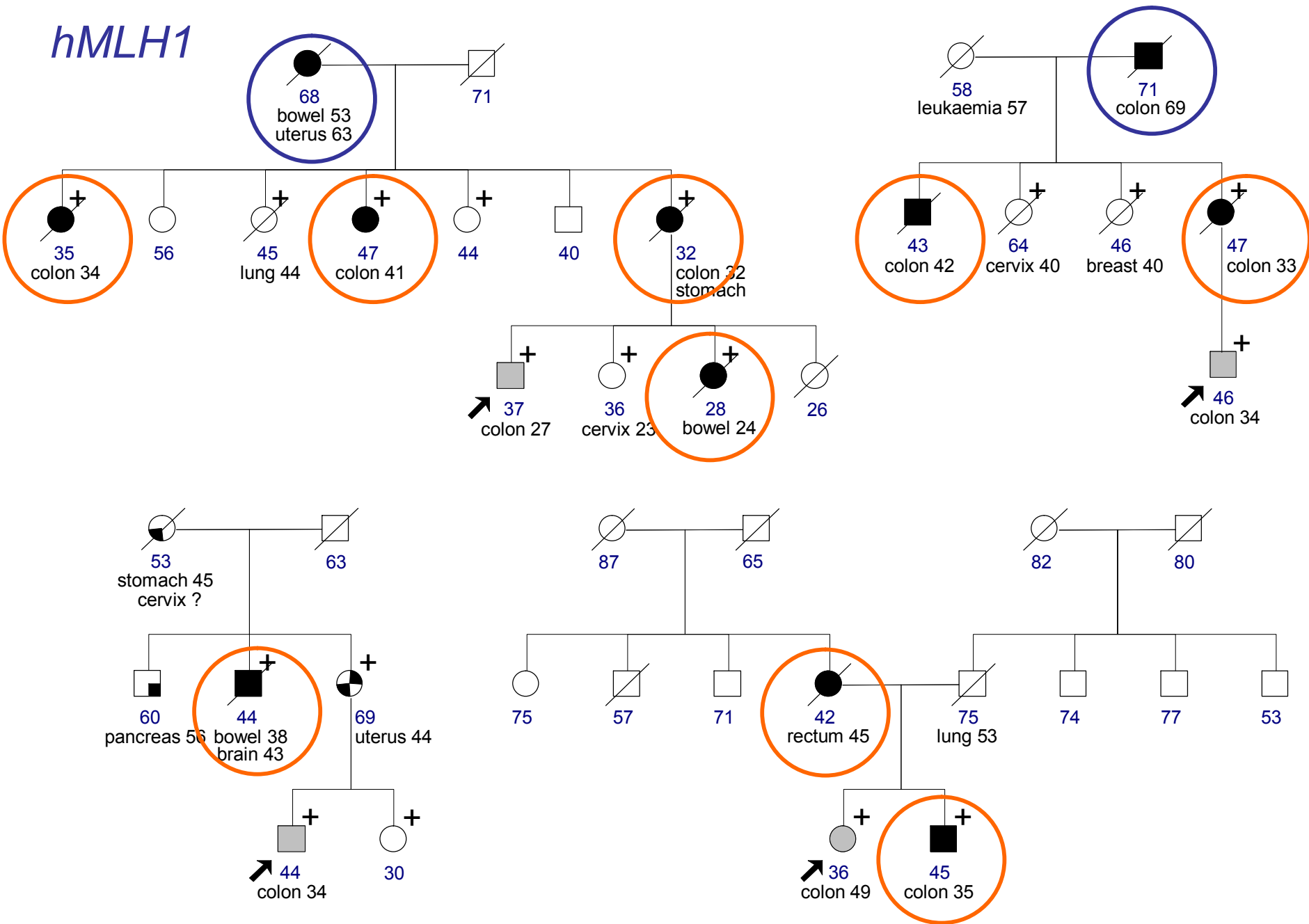
Mitchell et al, 2002

Victorian Colorectal Cancer Family Study

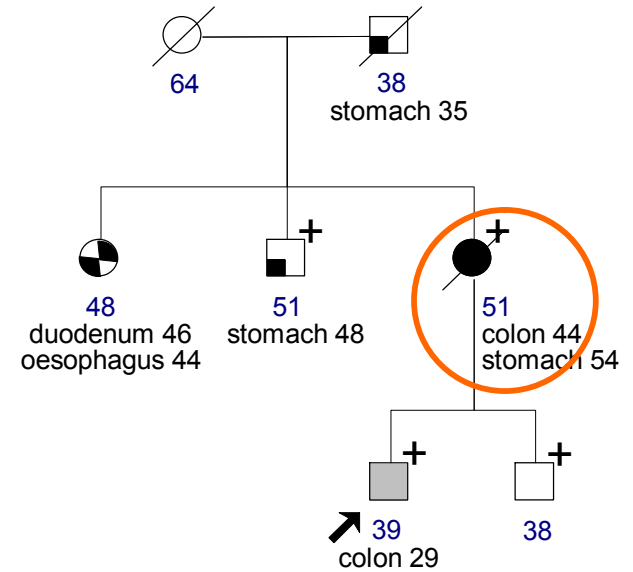
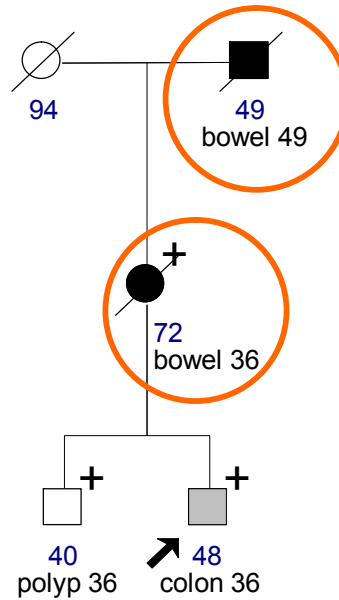
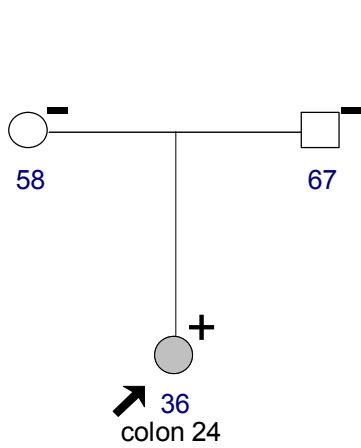
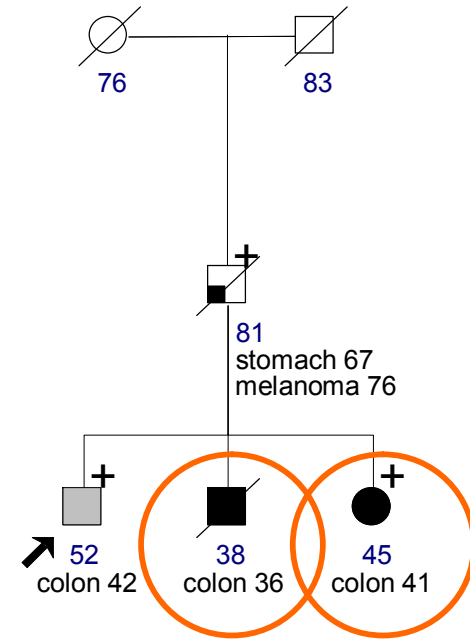
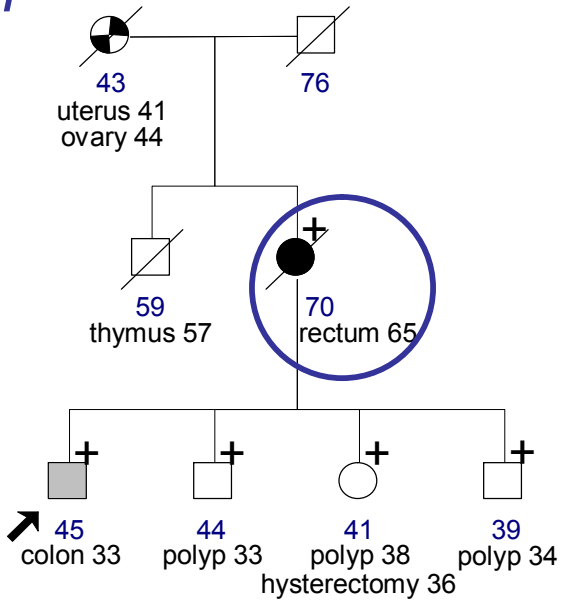


Gene	Mutation	Family History
<i>hMLH1</i> n=9	IVS8-1 G>C 1846 del AAG (C616) IVS8-11del25 2224delC (Q742X) IVS13-2 A>T 987del CAT (C330) IVS9+3insT del exons 4, 5 del exon 15	Amsterdam Criteria I Amsterdam Criteria I Amsterdam Criteria I Amsterdam Criteria I Amsterdam Criteria II Amsterdam Criteria II Amsterdam Criteria II HNPCC-related n.a.
<i>hMSH2</i> n=4	C>T Arg>Stop (C680) 1933C>T (P622L) 1957delGAAG (C630X) 2144del8 (G692X)	Amsterdam Criteria I Amsterdam Criteria I HNPCC-related None
<i>hMSH6</i> n=4	3341delC (T1085X) 3602insA (R1172X) 4045delGCAA (A1320X) 686C>A (S200X)	Amsterdam Criteria II Amsterdam Criteria II None None
<i>hPMS2</i> n=1	2267delAGAA (K748X)	None

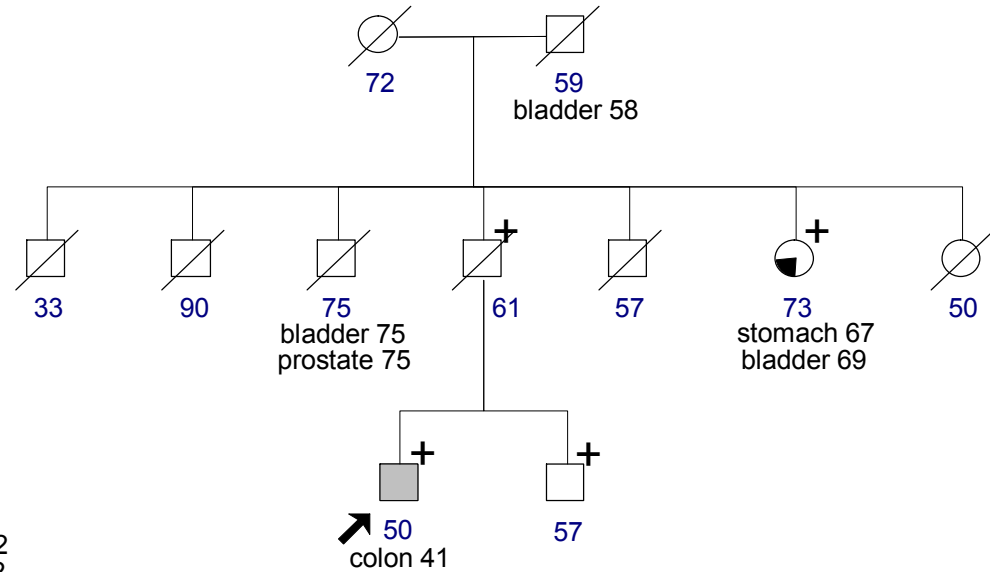
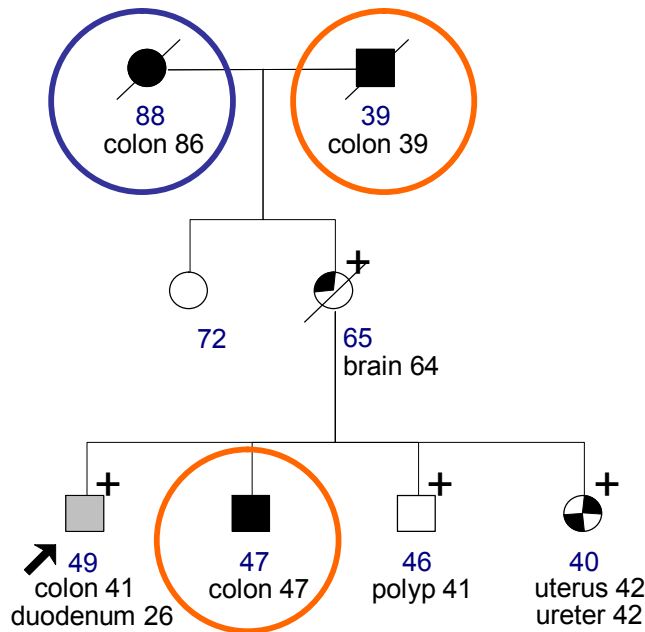
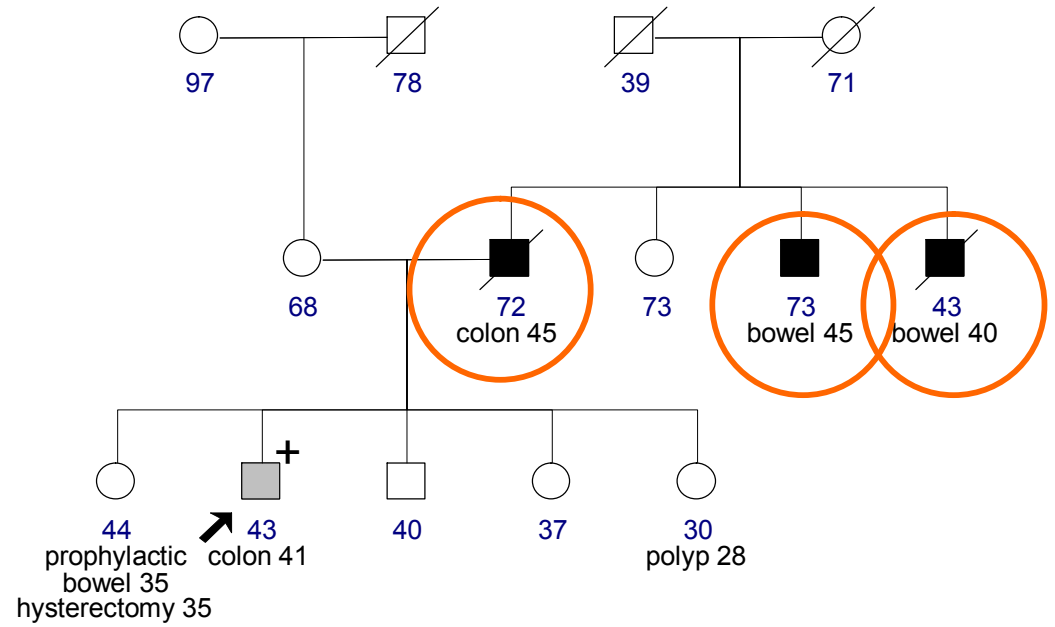
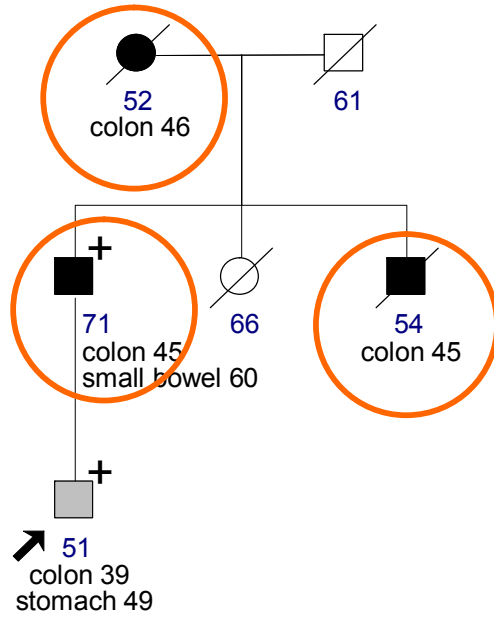
hMLH1



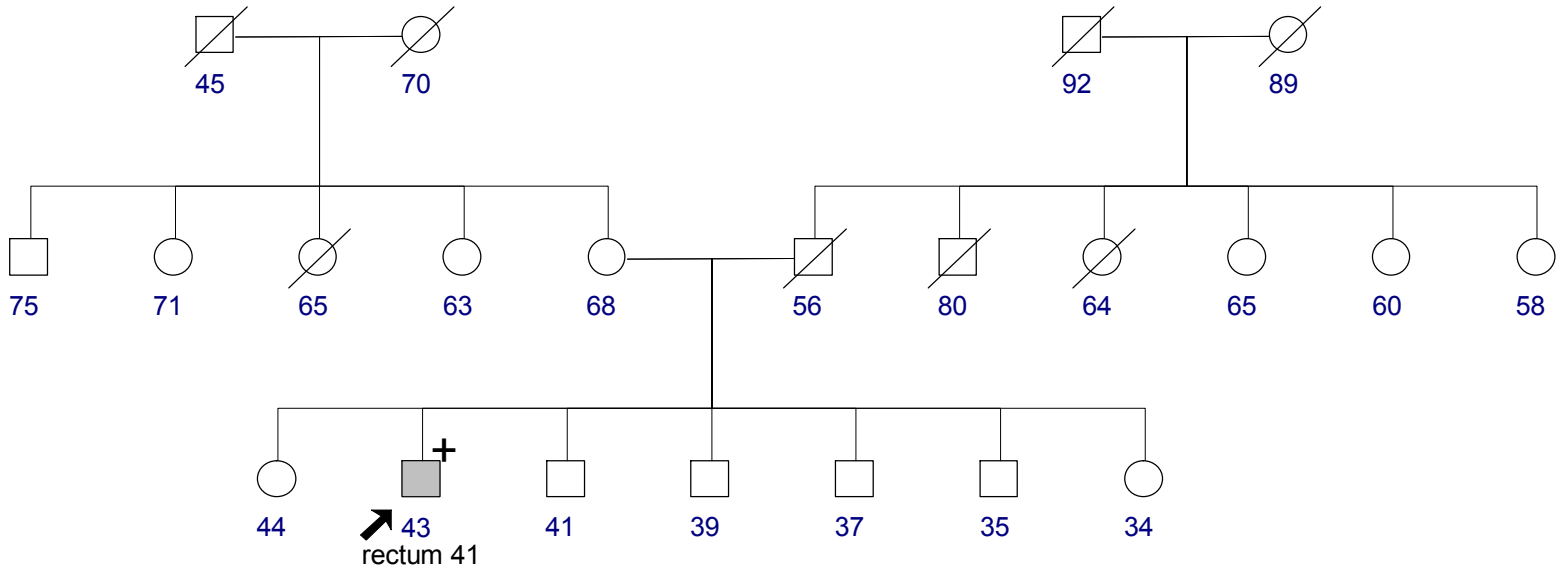
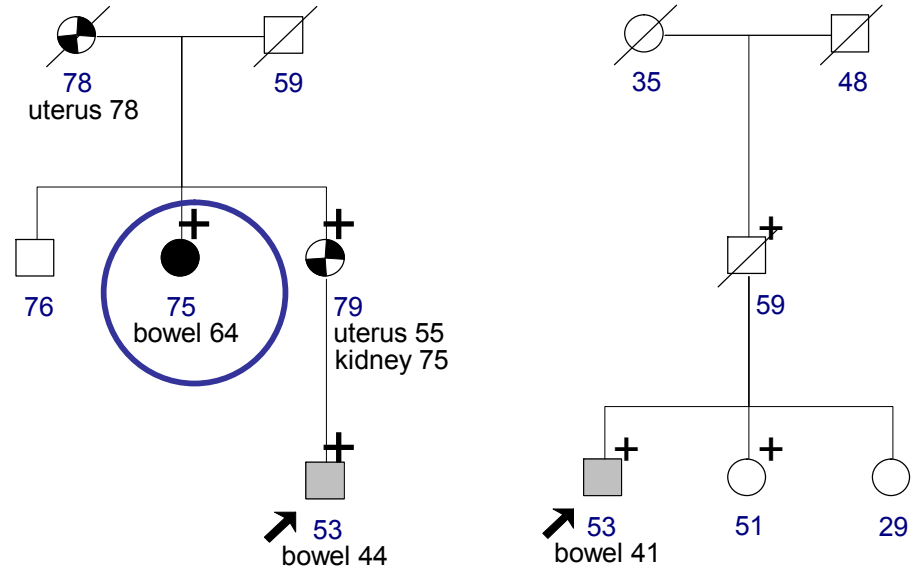
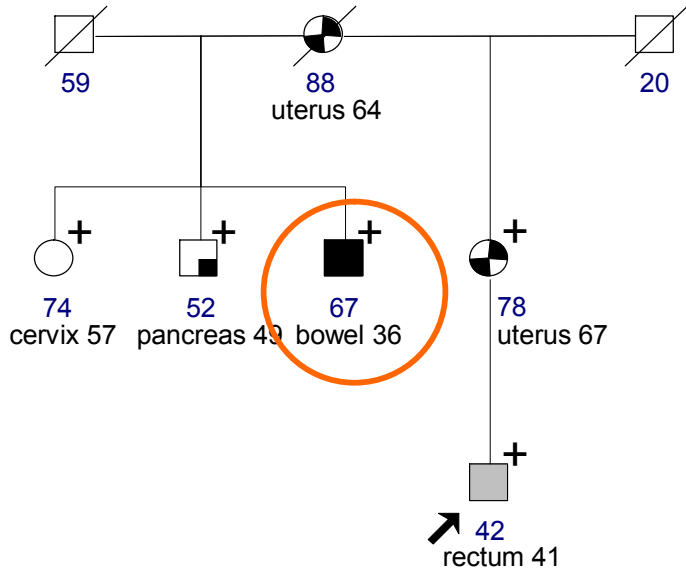
hMLH1



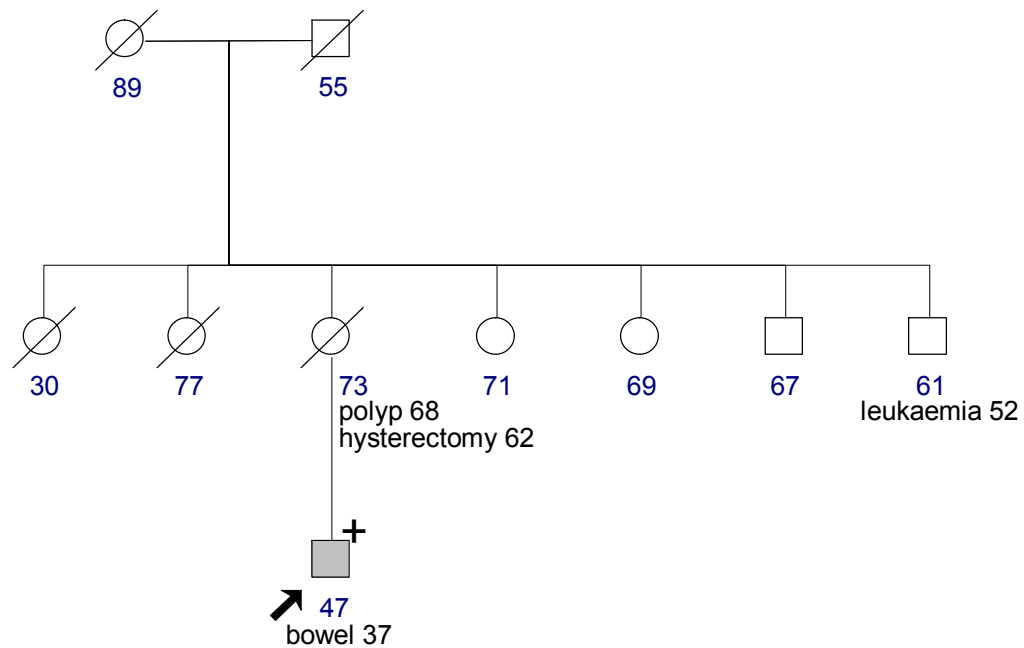
hMSH2



hMSH6



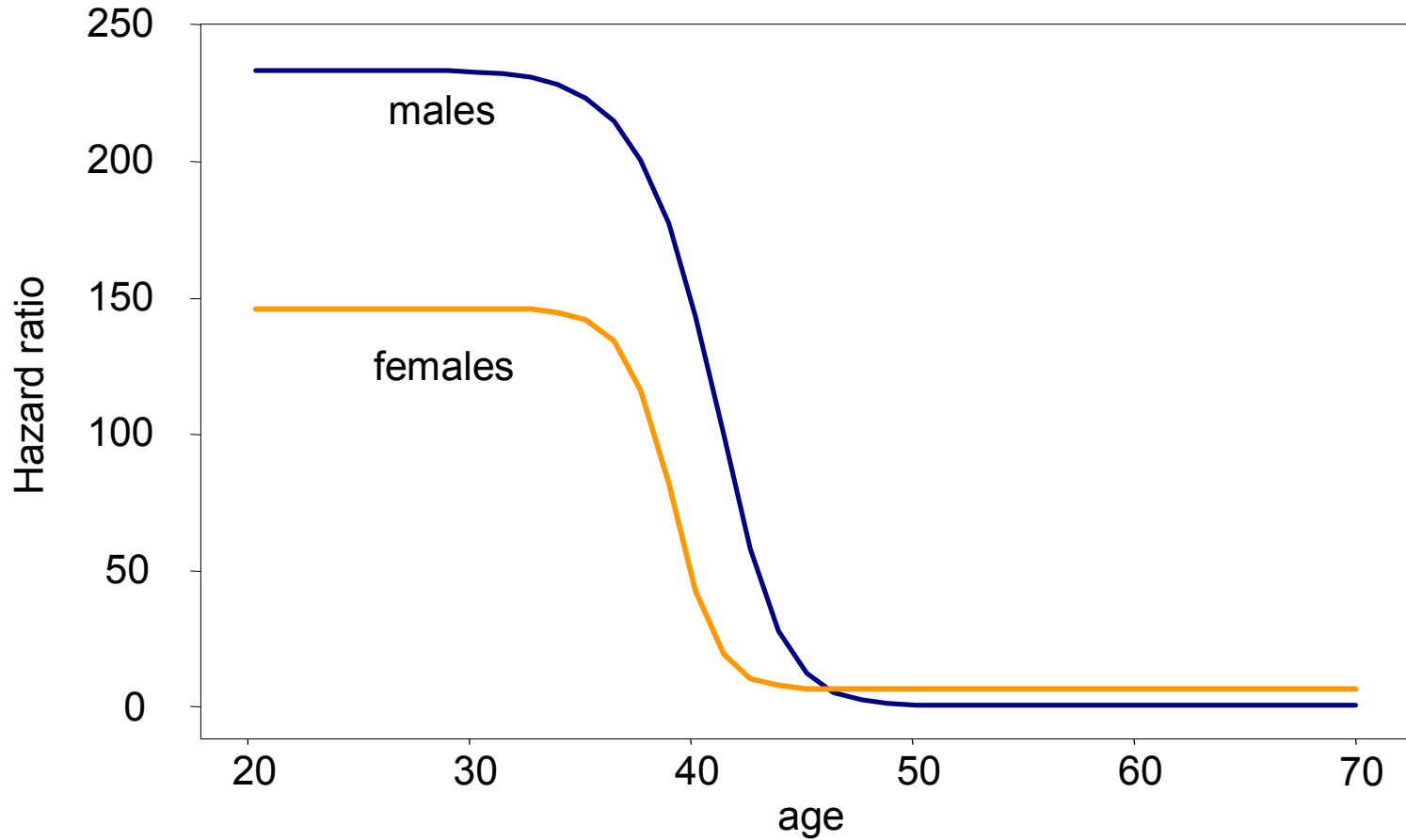
hPMS2



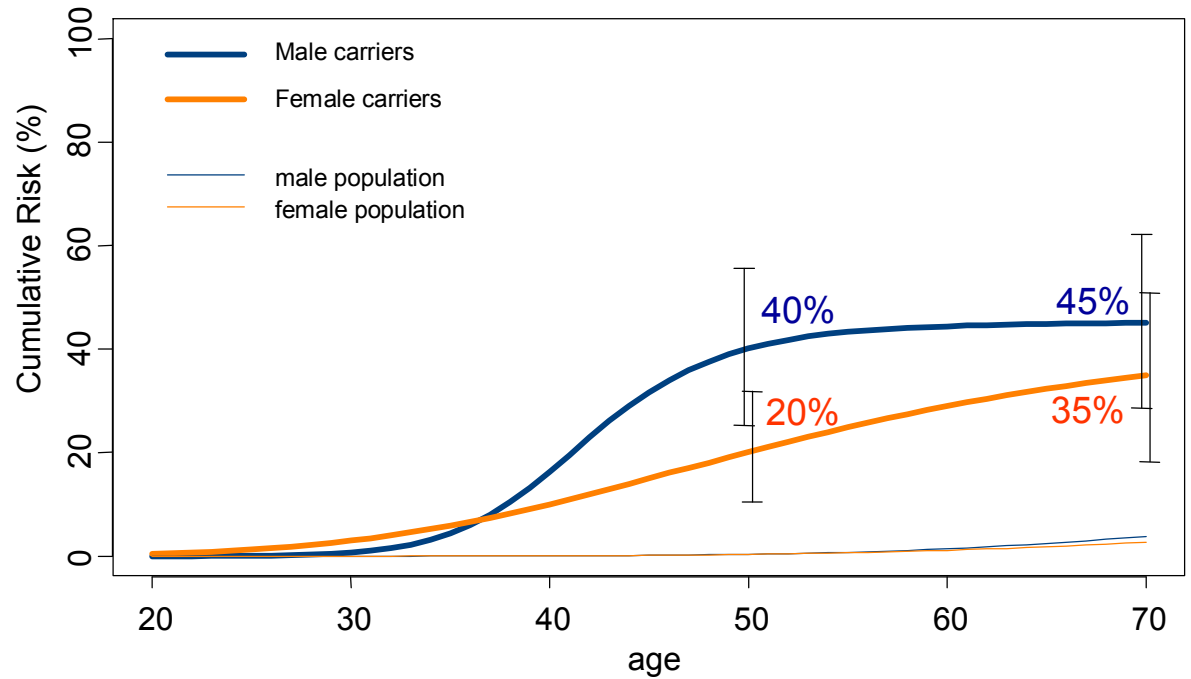
Estimation of Cancer Risk

- Risk and hazard ratios (ratio of age-specific incidence in mutation carriers to that in non-carriers) → MENDEL
- The joint likelihood of each family was expressed as a function of:
 - observed cancer status,
 - age at last contact, death or diagnosis (for unaffecteds, also age at surgery of a relevant organ or polypectomy),
 - carrier status (carrier, non-carrier or unknown)
- Risks and hazard ratios assumed to be logistic function of age
- Conditioned on ascertainment of proband (proband's cancers not included)

**Hazard ratio (risk in carriers compared to risk in the population) for CRC
in MMR mutation carriers**



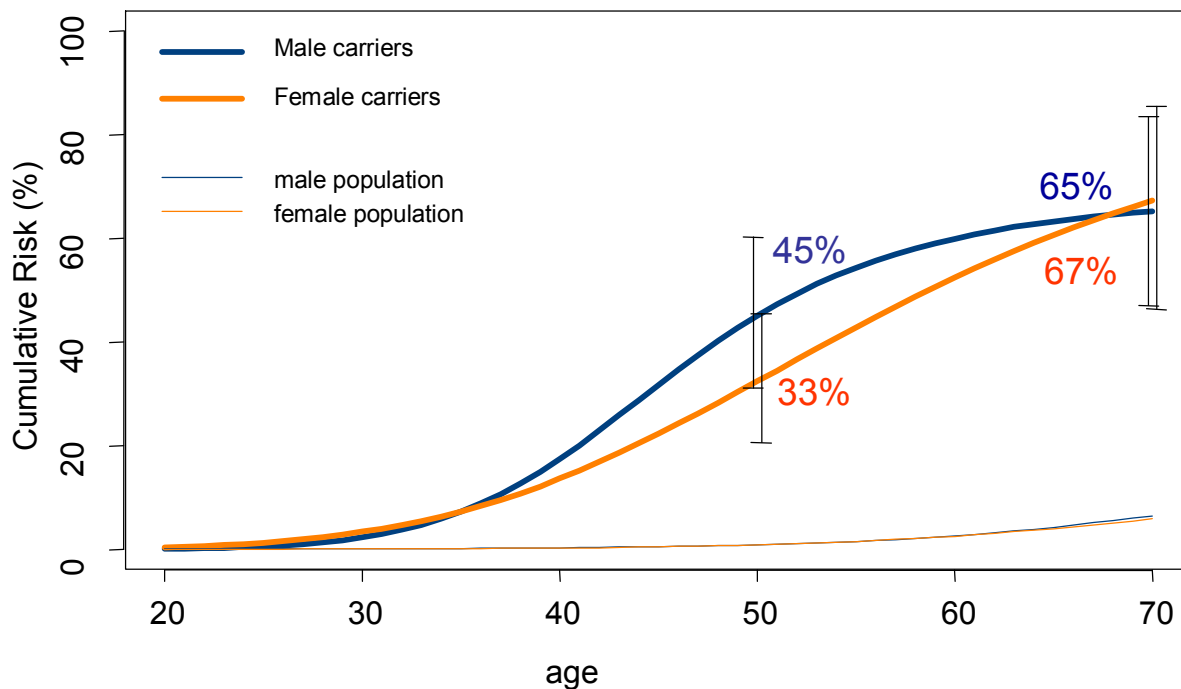
Cumulative risk of CRC in MMR mutation carriers



10-year risks of CRC given no disease at beginning of age period

	Male carriers	Male pop'n	Female carriers	Female pop'n
40 to 50 yrs	28%	0.3%	11%	0.2%
50 to 60 yrs	7%	1.0%	11%	0.8%
60 to 70 yrs	2%	2.4%	14%	1.6%

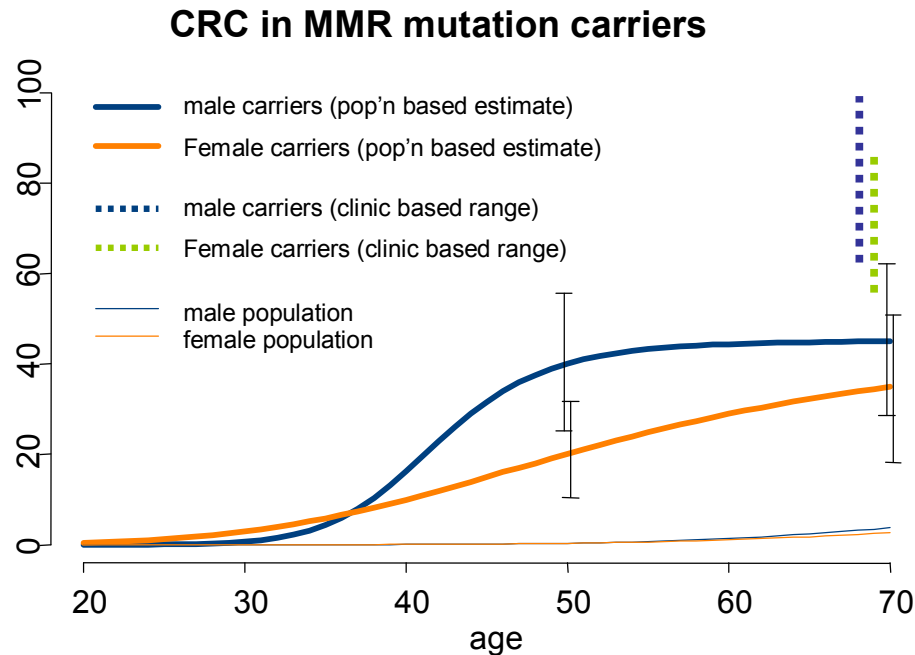
Cumulative risk of HNPCC-related cancers in MMR mutation carriers



10-year risks of HNPCC-related cancers given no disease at beginning of age period

	Male carriers	Male pop'n	Female carriers	Female pop'n
40 to 50 yrs	34%	0.5%	22%	0.6%
50 to 60 yrs	27%	1.8%	30%	1.7%
60 to 70 yrs	18%	4.1%	52%	3.4%

Conclusions



Risk is lower than previous estimates (probably)

Mutation effect strongest prior to age 50

Relevant for relatives of early-onset CRC case irrespective of other family history

Acknowledgements

Centre for Genetic Epidemiology,
The University of Melbourne

Christine van Vliet
James Dowty
John Hopper

Cancer Epidemiology Centre,
Cancer Council Victoria

Laura Baglietto
Graham Giles

Department of Colorectal Medicine and Genetics,
The Royal Melbourne Hospital

James St.John
Finlay Macrae

Department of Pathology,
The University of Melbourne

Melissa Southey
Andrea Tesoriero
Letitia Smith
Leeanne Mead
Simon Royce

Peter MacCallum Cancer Centre

Melanie Trivett
Kim Jennings
Jonathan Whitty

Queensland Institute of Medical Research

Michael Walsh
Melissa Barker
Joanne Young

Supported by the National Health & Medical Research Council of Australia and VicHealth, Australia.

