

# IT'S IN OUR FAMILY.....



## Hereditary Colorectal Cancer and Polyposis Syndromes



## NZ Familial GI Cancer Service

### What do we do?

- ▶ Offer assessment of bowel cancer risk for people with a family history of GI cancer
- ▶ Facilitate the diagnosis of hereditary cancer syndromes by confirming family history
- ▶ Offer surveillance recommendations
- ▶ Co-ordinate surveillance for high risk families
- ▶ Offer specialist management advice
- ▶ Provide information for families on familial GI cancer

Improving Outcomes for New Zealand Families

# Who should be referred?

- Those potentially at high risk per the NZ Guidelines for Surveillance and Management of groups at increased risk of CRC (ie: Category 3)
- Known or possible Lynch syndrome (HNPCC)
- Family history of other GI cancers eg; gastric cancers, pancreatic cancers
- Individuals with multiple polyps suggestive of a polyposis syndrome eg; Familial Adenomatous Polyposis (FAP or attenuated FAP), MYH Associated Polyposis (MAP), Serrated Polyposis Syndrome or Peutz Jeghers Syndrome

## NZ Guidelines Group Categories for CRC risk based on family history

Category 1: Slightly increased risk

Category 2: Moderately increased risk

Category 3: Potentially high risk





(risk above that of the general population)

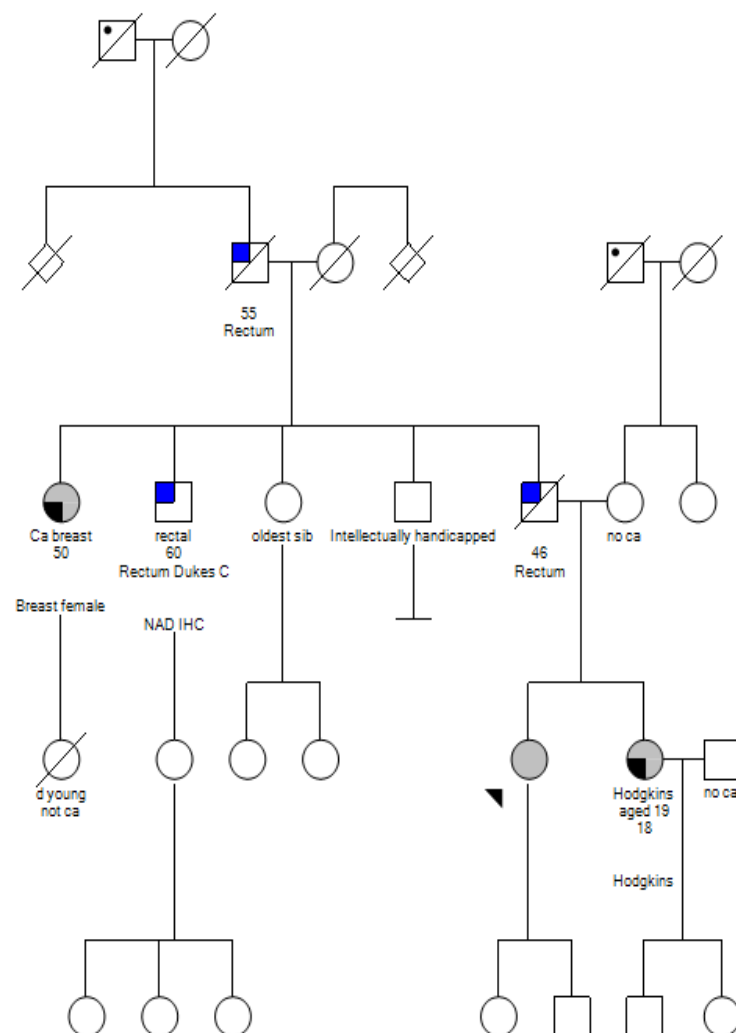
# What factors increase a person's risk of colorectal cancer?

- Age
- Personal history
- Family history

# What family factors increase our risk of colorectal cancer?

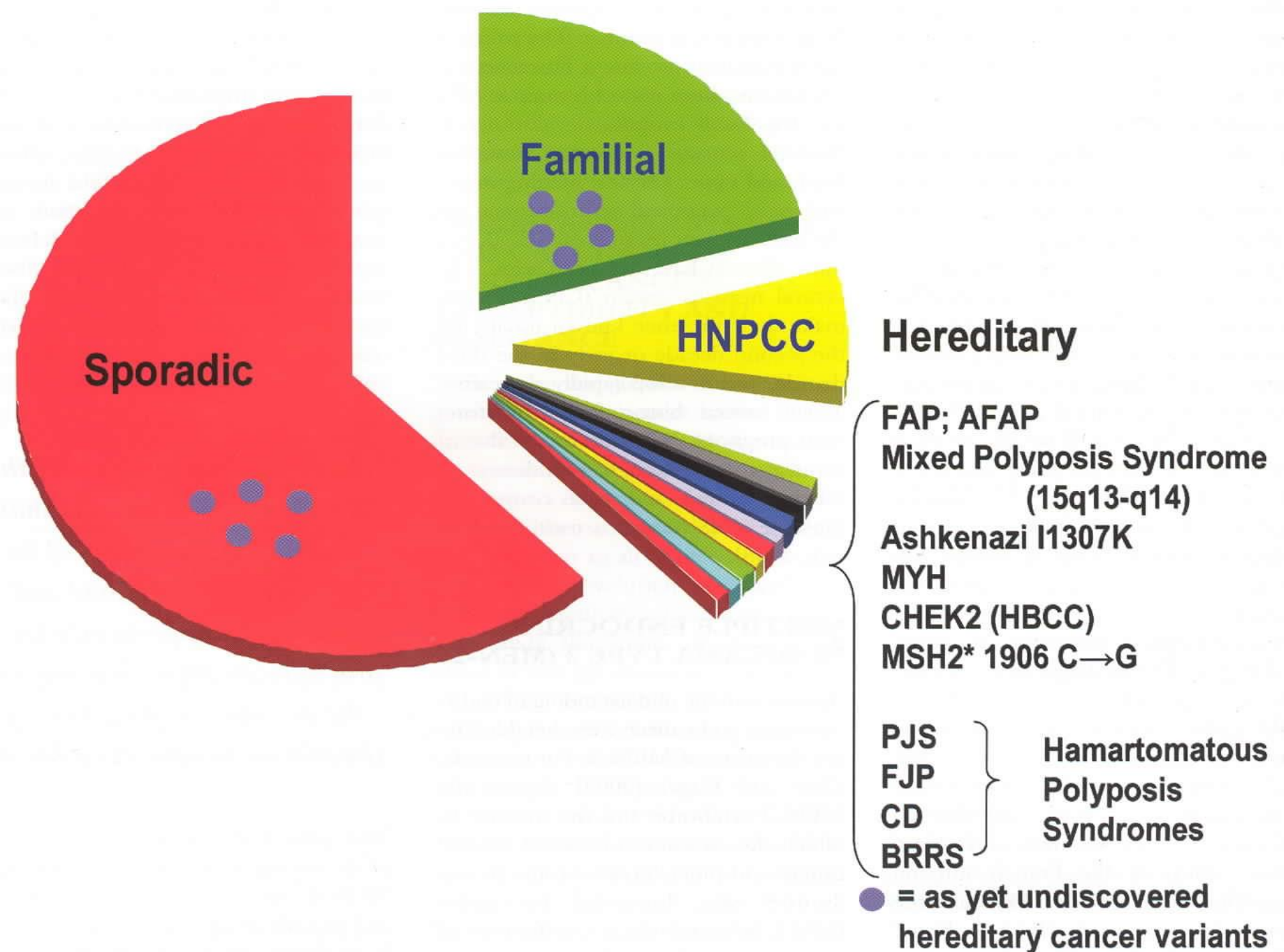
- Numbers of relatives diagnosed with CRC
- Age at diagnosis
- Degree of relationship to you

-  1.Type of cancer = Bowel
-  1.Type of cancer = Any Others
-  1.Unconfirmed cancer = Bowel
-  Surveillance consent = Accepted



## Category 3: Potential High Risk of Colorectal Cancer

- A family history of Familial Adenomatous Polyposis (FAP), Lynch Syndrome or other familial CRC syndrome
- One FDR plus two or more 2<sup>nd</sup> degree relatives (SDR) on same side of family diagnosed CRC at any age
- Two FDRs or one FDR and one or more SDRs on same side of family with CRC and one of them
  - - diagnosed under 55
  - - developed multiple bowel cancers
  - - developed an extracolonic cancer suggestive of Lynch Syndrome (uterine, ovarian, stomach, small bowel, renal pelvis, pancreas, brain)
- At least one FDR or SDR diagnosed with CRC in association with multiple bowel polyps
- Personal history of or one FDR with CRC diagnosed CRC under age 50 particularly where tumour immunohistochemistry revealed loss of expression of mismatch repair genes . Personal history of or one FDR with multiple bowel polyps



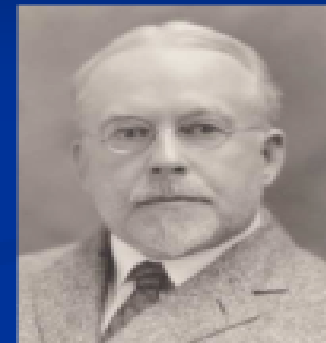
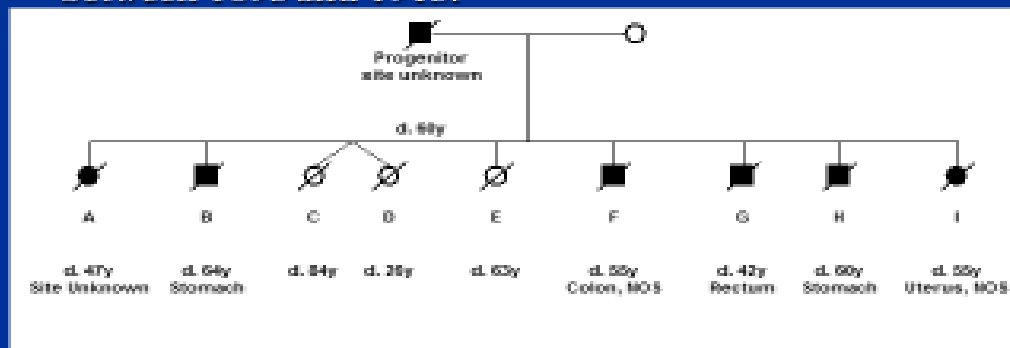
# Lynch Syndrome (HNPCC)

- Lynch syndrome historically known as Hereditary Non Polyposis Colorectal Cancer (HNPCC) is a rare inherited cancer condition that gives a high risk of bowel cancer and a smaller increased risk of certain other cancers.
- It is caused by mutations in the DNA mismatch repair genes which are genes responsible for correcting mistakes when DNA is copied.

# A Brief History of Lynch Syndrome

## Lynch Syndrome in Family “G”

- Dr. Aldred Scott Warthin, MD, PhD described “Family G” in a 1913 publication based on records ascertained from the University of Michigan hospitals between 1895 and 1913.



Douglas et al. (2005) History of Molecular Genetics of Lynch Syndrome in Family G; JAMA; Vol. 294 (17), 2198-2202

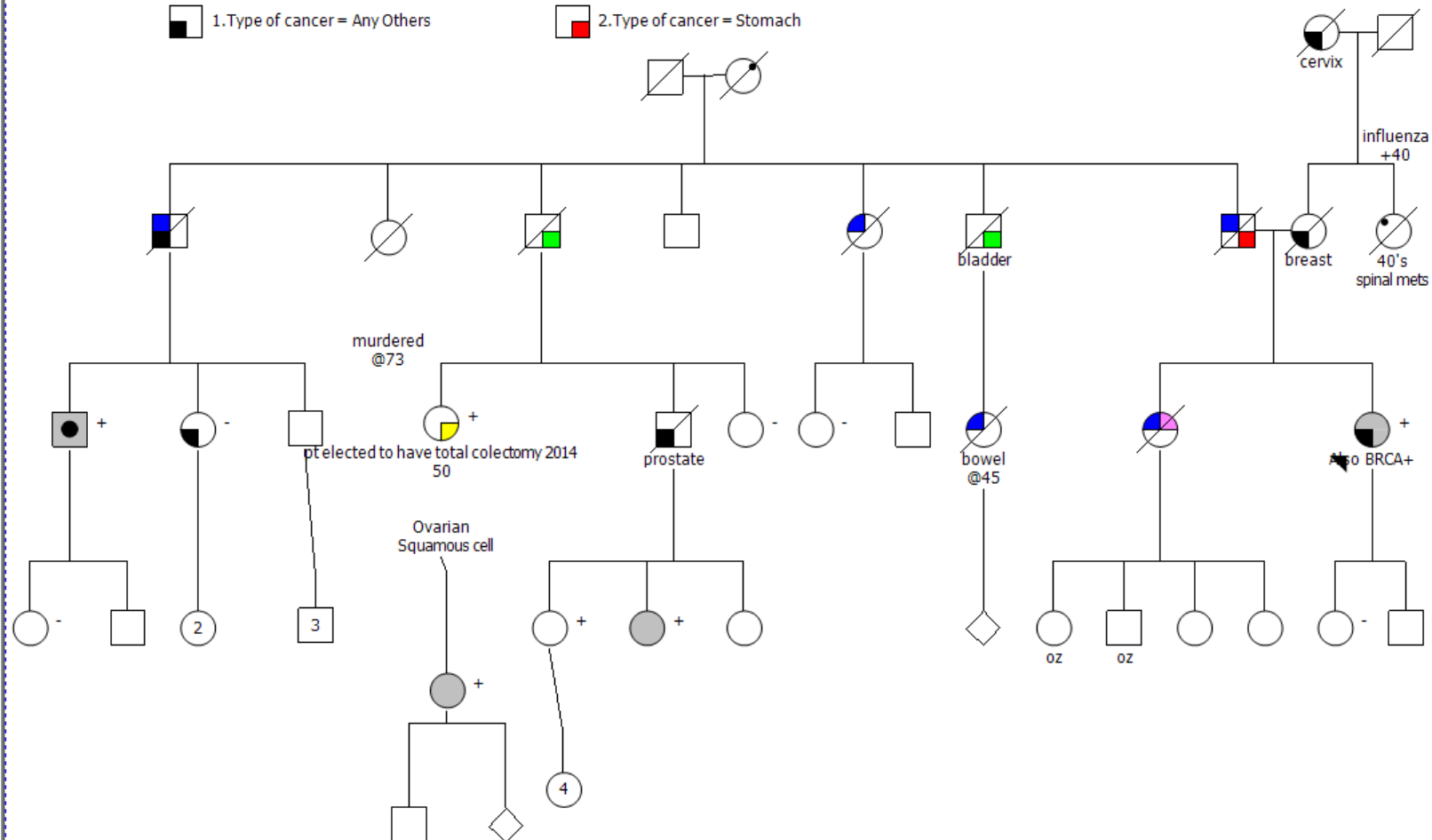
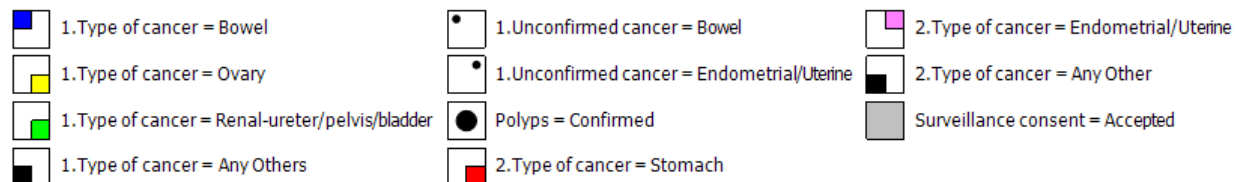
“Of the 48 descendants of the cancerous grandfather, 17 have died or been operated on for cancer. The preponderance of carcinoma of the uterus (ten cases) and of the stomach (seven cases) is very striking in the family history” Dr. Warthin, 1913.

# Hereditary Non Polyposis Colorectal Cancer

- Henry T Lynch followed up on this and other Nebraskan families in 1960's
- Condition named as above to distinguish it from FAP with multiple polyps



MSH2



# Risks of Colorectal and other Cancers in Lynch

Cancer	MLH1 to age 70 yrs <sup>1,2</sup>	MSH2 to age 70 yrs <sup>1,2</sup>	MSH6 to age 70 yrs <sup>3,2</sup>	PMS2 to age 70 yrs <sup>4</sup>	Lynch syndrome to age 70 yrs*	General population to age 85 yrs
Colorectal (male)	34%	47%	22%	20%	38%	10%**
Colorectal (female)	36%	37%	10%	15%	31%	6.6%**
Endometrial	18%	30%	25%	15%	33%	2 - 3%
Gastric	6%	0.2%	0	-	6%	1%
Ovarian	8-15%	8-15%	Low	-	9%	1 - 2%
Urothelial	0.2%	2.2%	0.7%	-	<3%	1%
Small Bowel	0.4%	1.1%	0	-	<3%	0.01%

\*This data does not take into account the impact of surveillance.

Data Source: NSW Central Cancer Registry 2008 final dataset and NSW Health Outcomes Information Statistical Toolkit (HOIST).






# Current Gastrointestinal Surveillance Recommendations for Lynch Mutation Carriers

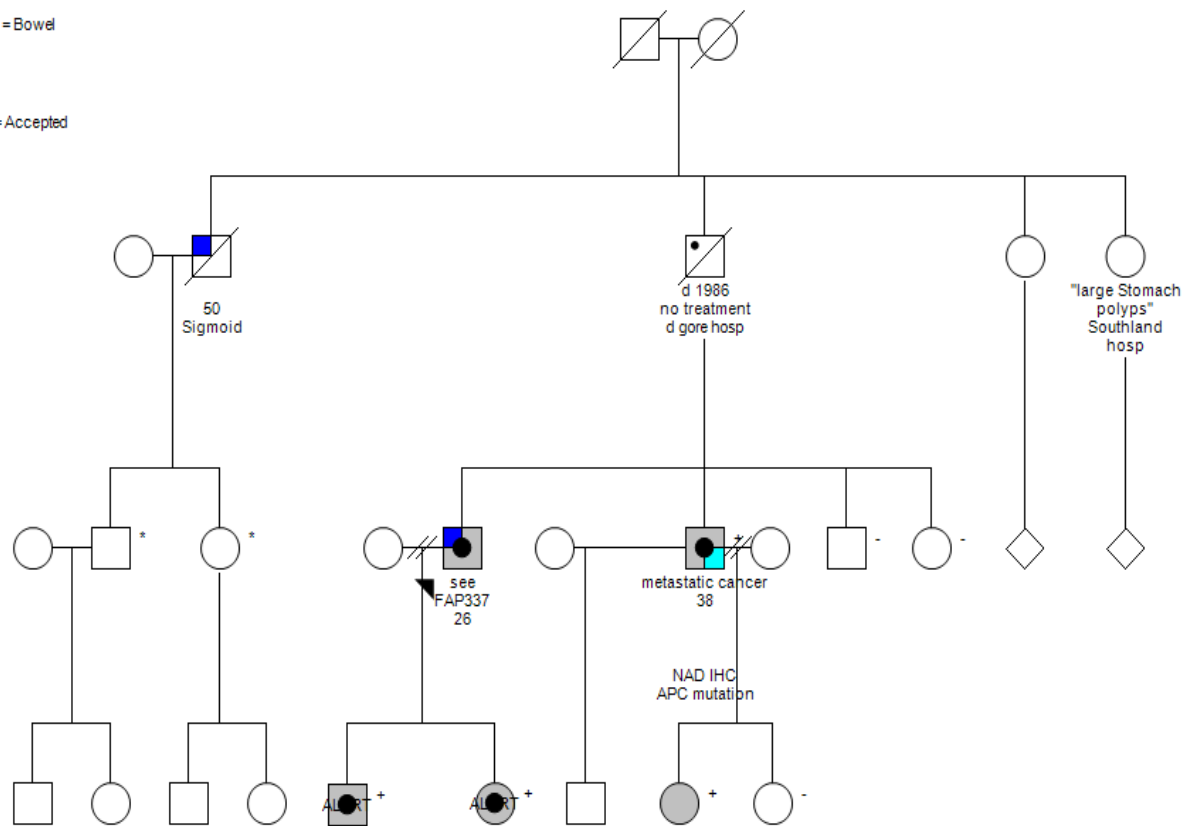
- ▶ Annual colonoscopy from the age of 25 years.
- ▶ It is recommended MLH1 and MSH2 carriers have a gastroduodenoscopy at 35 years with biopsies taken and eradication of H.Pylori.
- ▶ Further OGD in 3 years if any significant findings and if symptoms
- ▶ Consider gastroscopy for PMS2 and MSH6 carriers if significant family history of gastric cancer or symptoms

# Familial Adenomatous Polyposis (FAP)

- Caused by a mutation in the APC gene on Chromosome 5 (codes for protein that maintains normal cell growth and death rate)
- Characterized by 100s to 1000s of colorectal adenomas
- Risk of duodenal adenomas/adenocarcinomas
- Dominantly inherited from parent to child (50% chance for each child to inherit from an affected parent)
- 20 % are “de novo” mutations ie; occurs for first time in that person. No family history
- Penetrance is virtually 100% ie; carriers will develop CRC if surgery not done
- Onset of polyposis is in teenage years. Age of onset for colorectal cancer is late 30's - early 40's.
- Extracolonic features: thyroid cancer, Desmoid disease, hepatoblastoma in childhood, CHRPE, osteomas, supernumary teeth, epidermoid cysts

10/05/2010

-  1.Type of cancer = Bowel
-  1.Type of cancer = Small Bowel
-  1.Unconfirmed cancer = Bowel
-  Polyps = Confirmed
-  Surveillance consent = Accepted



1 of 1



# Surgery






- Mainstay of treatment is removing the large bowel before the adenomas have an opportunity to become malignant
- 3 options
  - Total colectomy and ileal rectal anastomosis (IRA)
  - Pan proctocolectomy and ileal anal pouch ( IPAA)
  - Proctocolectomy and ileostomy
  - Usually done in the late teenage years

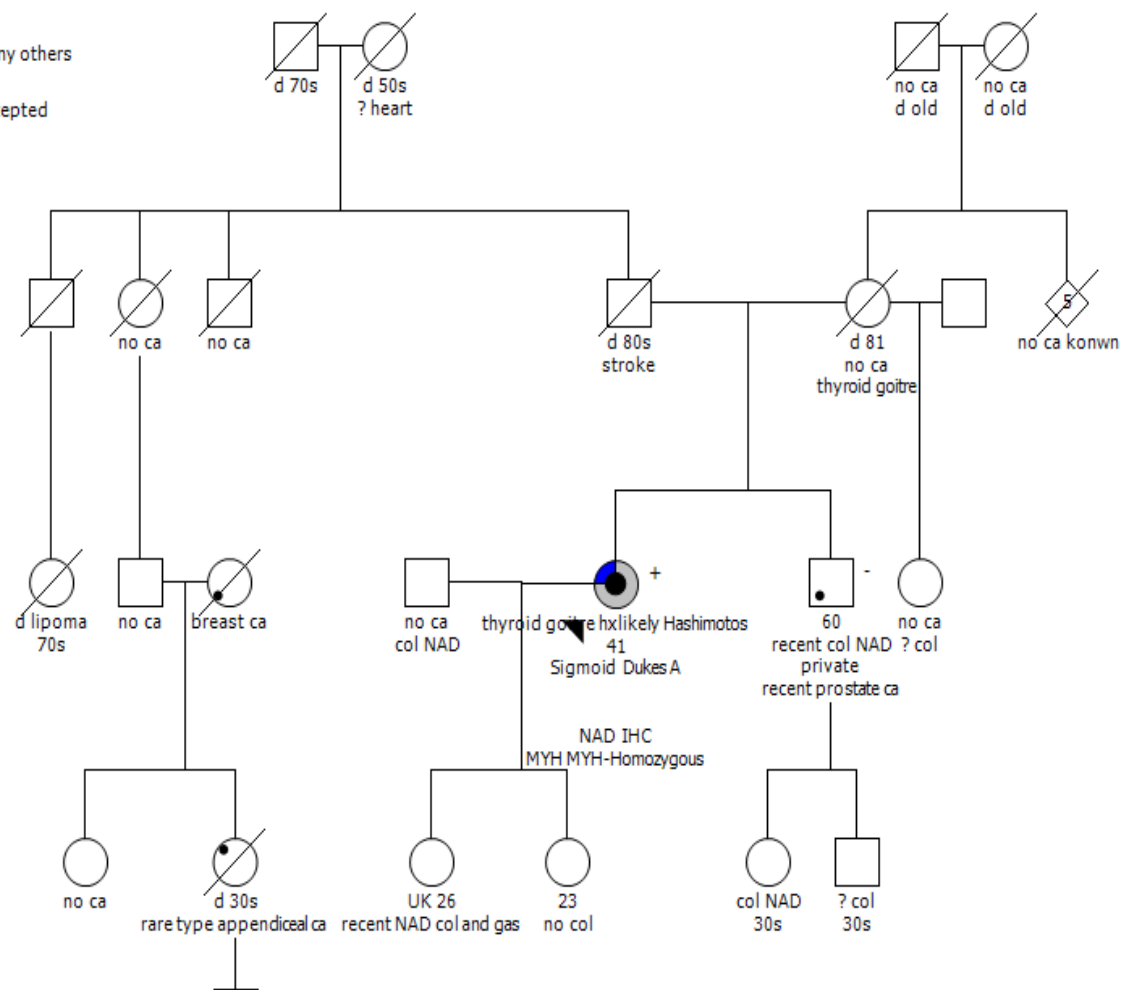
# Recommended surveillance post surgery

- Annual flexible sigmoidoscopy or pouchoscopy with removal of polyps
- Further surgery if indicated by polyp findings
- Chemoprevention if significant rectal adenomas: Sulindac or Celecoxib
- Gastroduodenoscopy starting at 25y with interval determined by number, size, type and dysplasia of duodenal polyps (Spigelmans Criteria)

# MutYH Associated Polyposis (MAP)

- Caused by homozygous mutations in both MutYH genes (base excision repair genes)
- Recessively inherited syndrome – must inherit a mutation from each parent
- Single generation affected
- Characterized by 10s to 100s of adenomas
- Polyp development starts age 20 s to 50s.  
Significantly incr risk of CRC
- Possible increased risk of duodenal adenomas

-  1.Type of cancer = Bowel
-  1.Unconfirmed cancer = Bowel
-  Polyps = Confirmed
-  1.Unconfirmed cancer = Any others
-  Surveillance consent = Accepted



# Treatment and Surveillance for MAP

- Based on numbers and size of polyps and age of individual at diagnosis
- Surgery vs colon surveillance with polyp removal
- Annual surveillance of colon
- Chemoprevention if significant rectal adenomas: Sulindac or Celecoxib
- Gastroduodenoscopy with interval as per Spigelman's stage

## Serrated Polyposis Syndrome (SPS) in a nutshell

- Syndrome in which multiple hyperplastic (HP) or serrated polyps are identified in the large bowel
- Estimated that 1:3000 people have this condition
- Associated with increased risk of bowel cancer but not usually other cancers apart from possibly pancreatic cancer at an older age
- Colonoscopy usually yearly in the initial years after diagnosis to control polyps. Aim to clear colon then extend interval
- Occasionally bowel resection is required if polyps are multiple, large or advancing dysplasia
- More common in individuals of European or Celtic descent
- Up to 50% of individuals with SPS have family history of CRC suggesting a genetic or inherited cause

# Criteria for Diagnosis of SPS

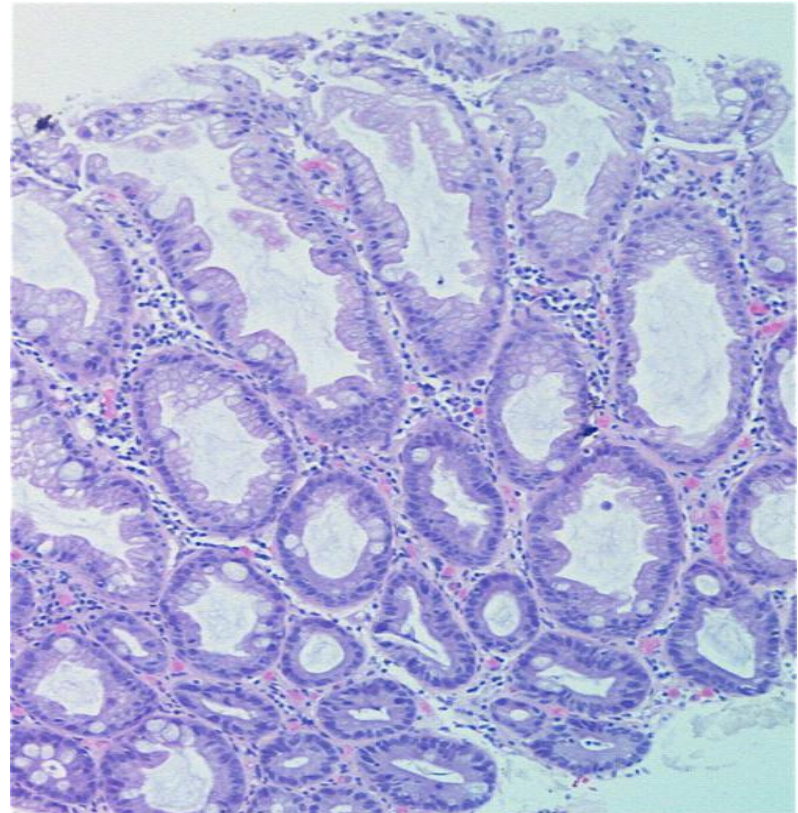
- 20 hyperplastic or serrated polyps throughout the colon (technically does not include the rectum)
- OR
- At least 5 such polyps beyond the distal bowel (transverse, ascending, caecum) and 2 are 10mm or larger
- Cumulative count allowed so may meet SPS diagnosis criteria after several colonoscopies

# Serrated Polyps

Group of polyps with variable malignant potential – includes –

- hyperplastic polyps
- sessile serrated adenomas
- serrated adenomas

# Hyperplastic polyps



# Sessile Serrated Adenomas (=Sessile Serrated Polyp)

**A**



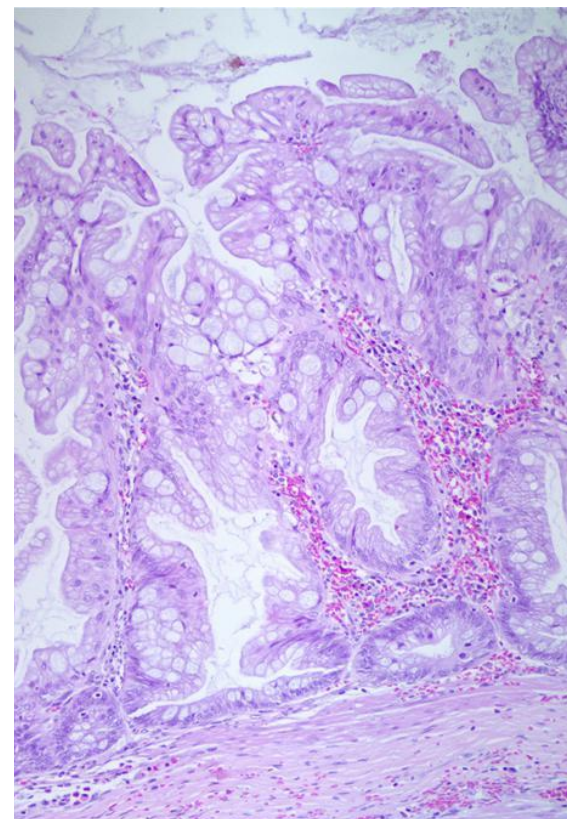
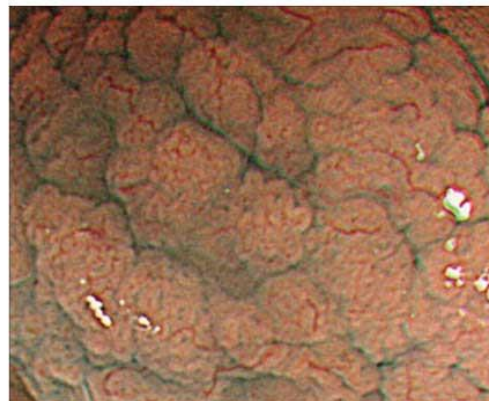
**B**



**C**



**D**



# Recommendations for individuals affected with SPS

- Frequent colonoscopy until polyps controlled then extend interval as per results of each procedure. Generally no less often than 3 yearly
- Occasionally surgery is required if polyp load high
- Advise smoking cessation as cigarette smoking is associated with increased polyp numbers
- Referral to Genetics of Serrated Neoplasia study (GSN) : Aiming to identify the genetics associated with SPS. Eligible if diagnosed with SPS and under 70y

## Recommendations for FDRs of those diagnosed with SPS

- 5 fold increase in risk of CRC compared to general population
- Increased risk of developing SPS themselves
- Recommended surveillance: 5 yrly colonoscopy from age 40 or from 10 yrs younger than the youngest age at diagnosis of CRC or SPS in the family

# Acknowledgements

- NZ Guidelines Group – Guidance on Surveillance for People at Increased Risk of colorectal Cancer 2012
- [www.eviQ.org.au](http://www.eviQ.org.au) Cancer Genetics
- [www.nzfgcs.co](http://www.nzfgcs.co) .NZ Familial GI Cancer Service
- Colonic Polyps Sept 2014 Dr Teresa Chalmers-Watson
- FAP – Introduction 2014 Mr Chris Wakeman

# Questions??







Improving Outcomes for New Zealand Families