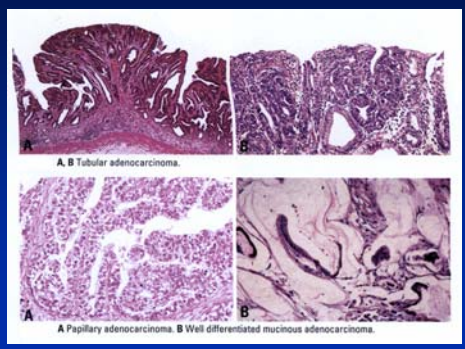
Genetic Markers of GI malignacy

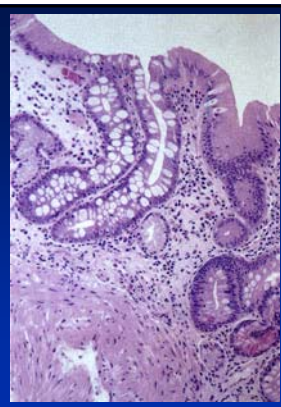
David Huntsman
Genetic Pathologist BCCA
dhuntsma@bccancer.bc.ca

Hereditary diffuse gastric cancers as a model to discuss

- The genetic basis of GI cancer susceptibility
- The clinical spectrum of familial GI cancers
- The clues for the identification of high risk families
- The benefits of aggressive management
- Issue for counseling: ie: non penetrance and new mutations

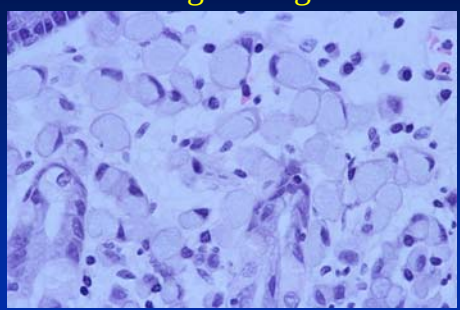
Intestinal type gastric cancer





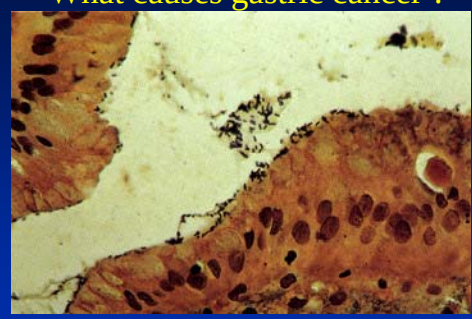
Intestinal metaplasia: The precursor lesion for intestinal type gastric cancers

Diffuse or signet ring carcinoma



Precursor lesion not known

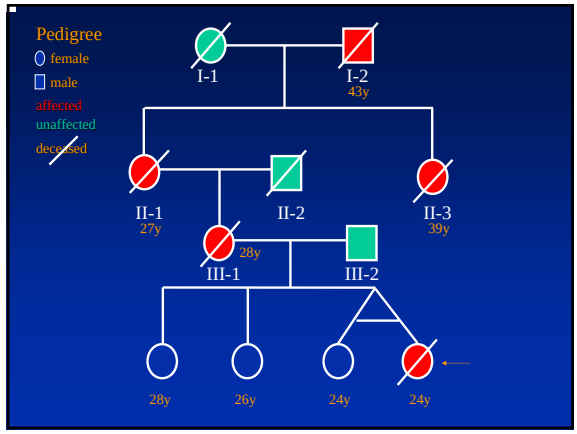
What causes gastric cancer ?

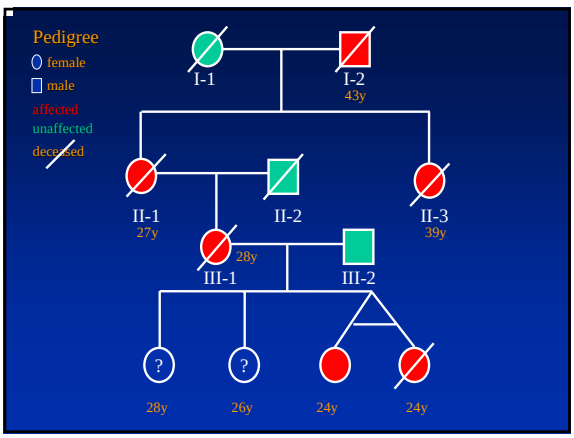


Helicobacter pylori infection may be a prerequisite for gastric cancer development

Gastric Cancer: Familial Risk

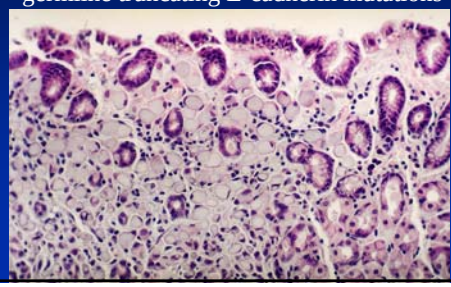
- Relative risk for first degree relatives 2.09 (breast 1.83, colon 2.67)
- Gastric cancers seen in HNPCC kindred (79% intestinal) and Li Fraumeni syndrome
- Autosomal dominant susceptibility for diffuse gastric cancer has been known as clinical entity for many years



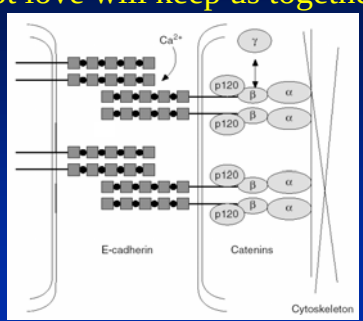


E-cadherin in HDGC

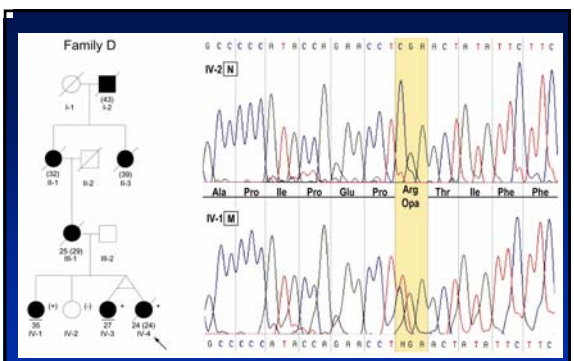
- In 1998 Parry Guilford described three Maori kindred with HDGC on the basis of germline truncating E-cadherin mutations

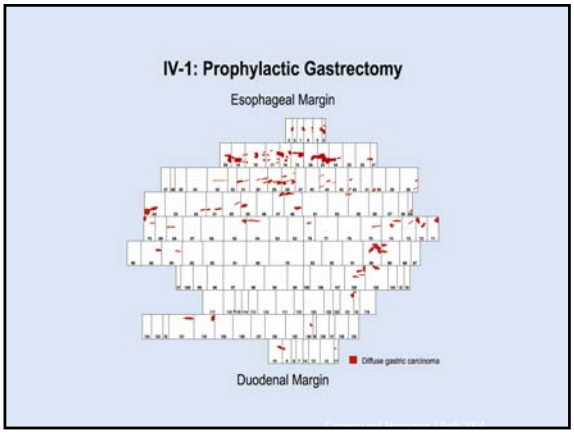


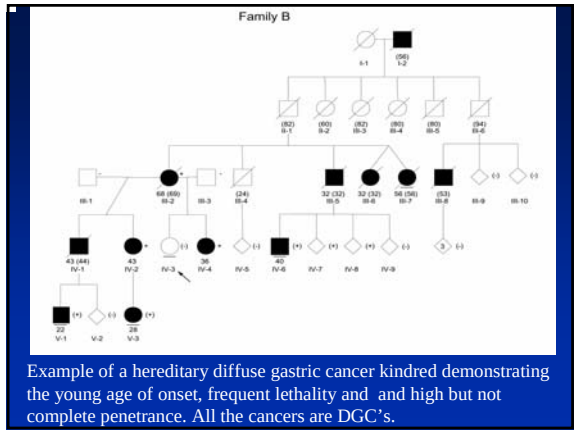
E-cadherin (CDH1): not love will keep us together



Loss of E-cad is a defining feature of both DGC and lobular breast cancer



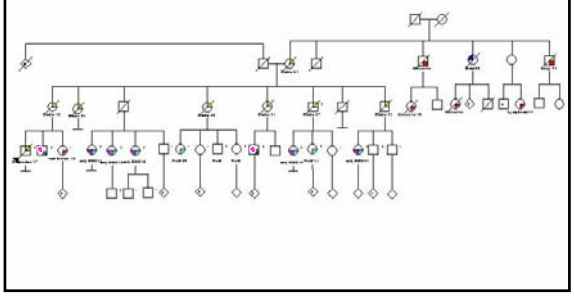




Example of a hereditary diffuse gastric cancer kindred demonstrating the young age of onset, frequent lethality and and high but not complete penetrance. All the cancers are DGC's.

A recurrent E-cadherin mutation
C1003T truncating mutation : family 2

8 gastrectomies in mutation carriers 7 with cancer
1 gastrectomy performed before genetic testing



Clues to proband identification for any hereditary cancer syndrome

- Unusual patient: young age
- Unusual history: multiple tumours of the same type or from the tumour spectrum of a HCS (lobular breast and DGC)
- Unusual pathology (In-situ SRC)
- Family history

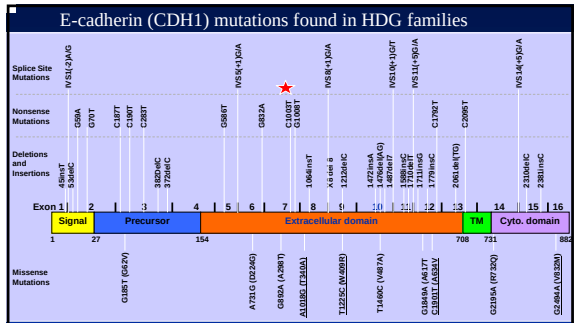
Apply to hereditary diffuse gastric cancer

Criteria for CDH1 mutation testing modified to reflect current data.

Modified Testing Criteria	1.Family with two or more cases of GC, with at least 1 DGC diagnosed before the age of 50. (>30%)* 2.Family with multiple LBC with or without DGC in first or second degree relatives (unknown)* 3.Isolated individual diagnosed with DGC at less than 35 years from a low incidence population (>10%)* 4.Isolated personal history of both DGC and LBC (unknown)*

*Percentage of expected positive results.

E-cadherin (CDH1) mutations found in HDG families



60 pathologic mutations described to date

Incidence of Cancer in CDH1 Mutation Carriers

- Data from 476 individuals from 11 families
- Life time cumulative risk 67% for men and 83% for women
- Lifetime risk for breast cancer 39% (RR6.6) gastric cancer risk five times that of breast cancer
- Potential association with signet ring carcinoma of the colon
- Note : expect the penetrance figures to drop

Management options for germline E-cadherin mutation carriers

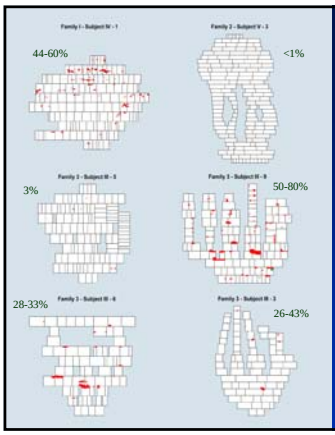
- A) Prophylactic gastrectomy
- B) Endoscopy (chromoendoscopy)
- C) Watch and wait

Endoscopy: chromoendoscopy

- Recommended twice a year for at risk individuals from families who tested negatively and mutation pos individuals from missense mutation families
- May buy time before considering surgery
- Best option for elderly or poor surgical risks
- Unlikely to detect all cancers but may detect cancers before they are clinically relevant

Proph gastrectomy

- Reasonable option for unaffected mutation positive individuals
- To be performed by expert surgeon (?definition) after counseling by surgeon and dietician
- Total gastrectomy essential
- Mortality <1% (best guess)

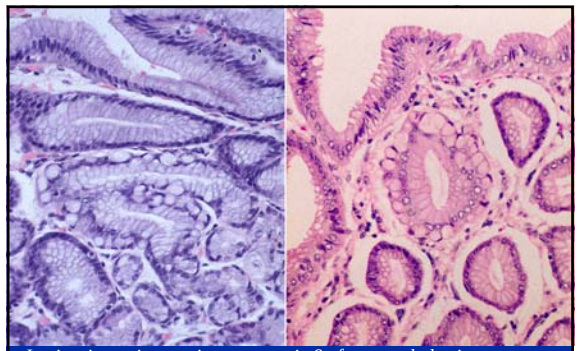


Currently 22/23 prophylactic gastrectomies reviewed in total had occult DGC's

Maps of 6 prophylactic gastrectomy specimens. Cancers shown in red.

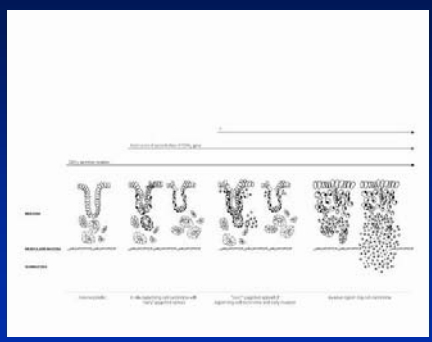
H. pylori infection present in NZ cases only

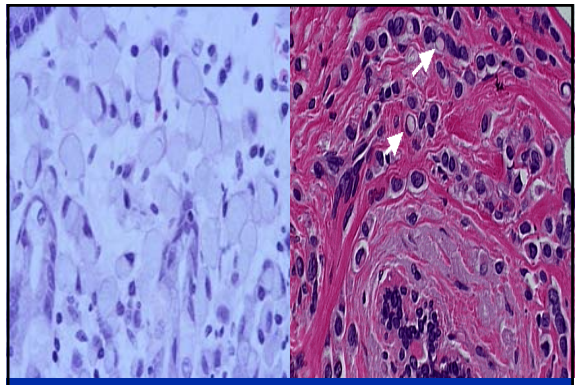
All cancers were very superficial, the rate of progression of these lesions and the the secondary mutations required for invasion of the muscularis propria are unknown



In-situ signet ring carcinomas seen in 8 of ten prophylactic gastrectomy specimens: ? The precursor lesion for all diffuse gastric cancers

A model of the development of diffuse gastric cancer





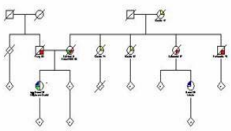
Diffuse gastric cancer Lobular breast cancer

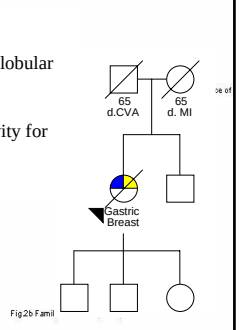
Breast cancer risk

Approx 40% lifetime risk of developing lobular breast cancer

Mammography has questionable sensitivity for lobular breast cancer

MRI is likely more sensitive and thus is recommended (evidence anecdotal)



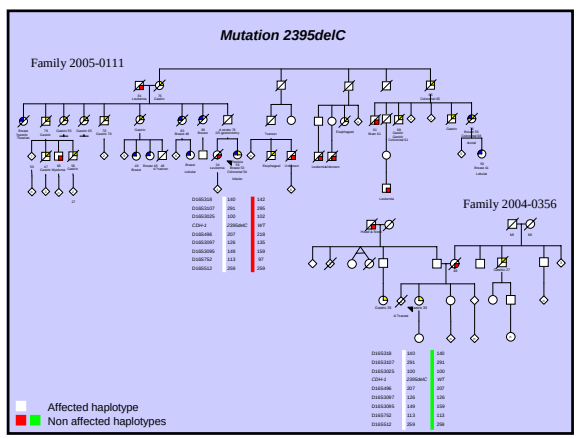


Lobular breast cancer summary

- In CDH1 >90% of breast cancers in proven mutation carriers are lobular
- Parts of many families have more breast than gastric cancers
- As all families so far were ascertained through their gastric cancer have we underestimated the importance of germline E-cadherin mutations in lobular breast cancer susceptibility?

HDGC: knowledge deficits

- What causes the cancer susceptibility in the mutation negative families?
- Are all mutations equally penetrant or do phenotype genotype correlations exist?
- Can endoscopy or chromoendoscopy be relied upon to detect gastric cancers before they metastasize ? (maybe not)
- Could aggressive H. Pylori eradication reduce cancer risk? (no)
- Once the gastric cancer risk is removed will other cancer risks emerge?
- How should the lobular breast cancer risk be handled? (MRI)
- Could chemoprevention help, for instance with de-methlyating agents or tamoxifen?
- Will E-cad mutations be found in families with LBC but no gastric cancer?
- What is the real penetrance?



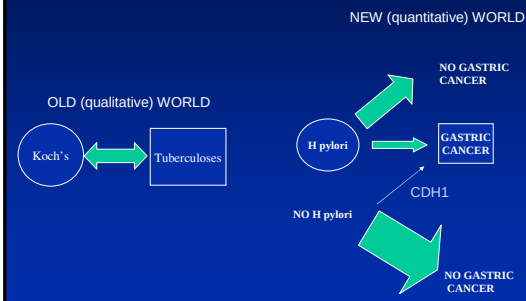
Placentia bay family

- 29 gastric cancers
- 11 breast cancers
- Expanding rapidly
- Ideal for penetrance studies
- Gene environment interactions

Clinical objectives

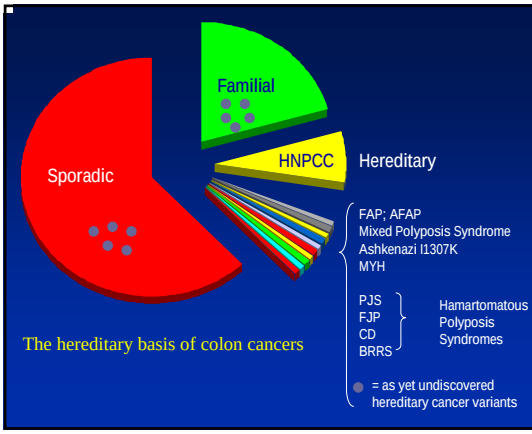
- Evidence based management guidelines
- Through education reducing the number of young people who have to develop cancer in a family before a referral is triggered and cancer risk reduction strategies are implemented

Necessary and sufficient cause



Clues to proband identification for any hereditary cancer syndrome

- Unusual patient: young age
- Unusual history: multiple tumours of the same type or from the tumour spectrum of a HCS.
- Unusual pathology:
- Family history
- For every GI cancer there is a hereditary cancer syndrome

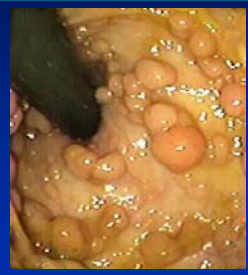


Genetics of hereditary CRC

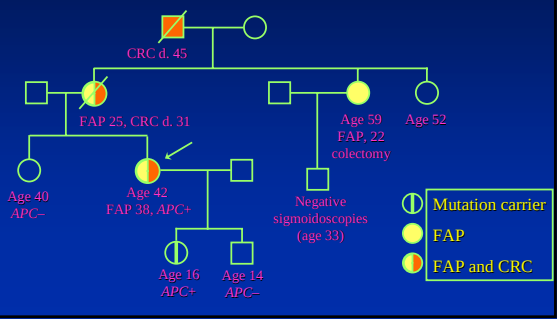
- FAMILIAL ADENOMATOUS POLYPOSIS (FAP)
- Hereditary non-polyposis colon cancer syndrome HNPCC or Lynch syndrome
- Others (attenuated FAP etc)
- Clinical followup of high risk families saves lives
- Genetic testing stratifies risk within families and therefore saves money (this is preventative medicine and therefore difficult to fund)

Clinical Features of FAP

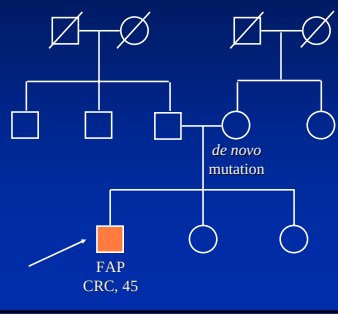
- Estimated penetrance for adenomas >90%
- Risk of extracolonic tumors (upper GI, desmoid, osteoma, thyroid, brain, other)
- Untreated polyposis leads to 100% risk of cancer



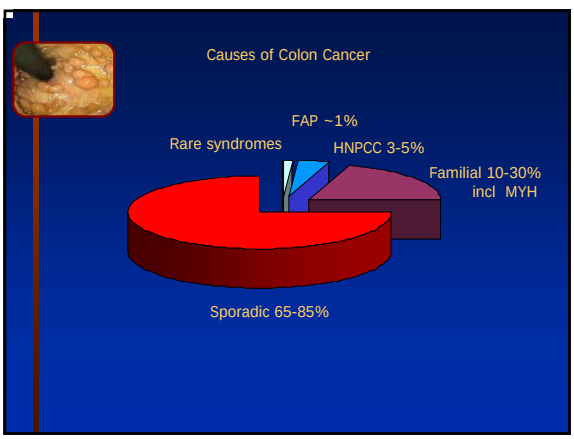
FAP Family With *APC* Mutation

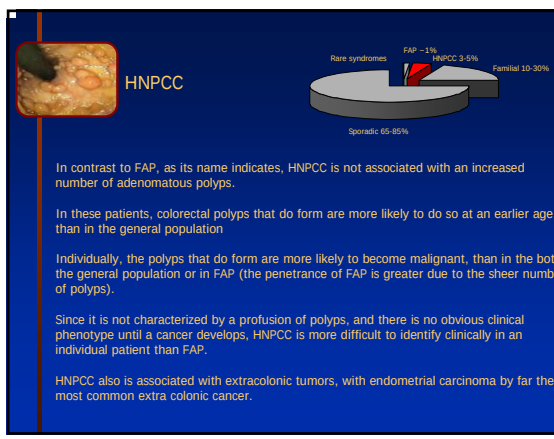


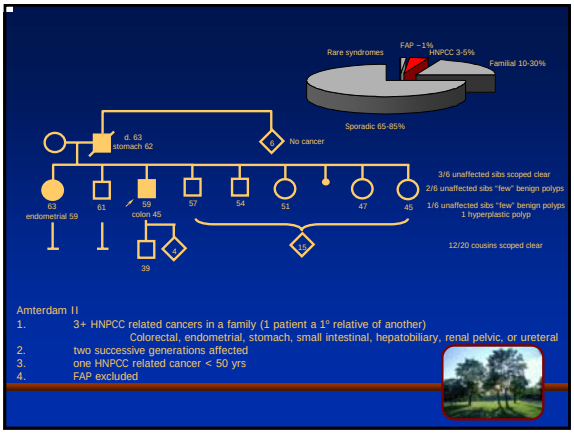
De Novo Germline Mutations in FAP *when it quacks like a duck*



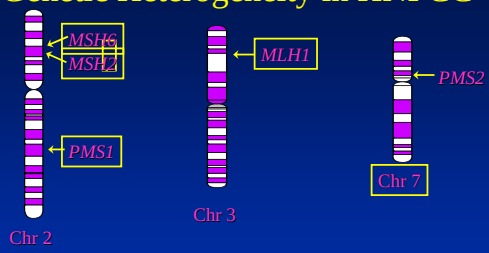
De novo germline mutations occur in ~30% of FAP cases





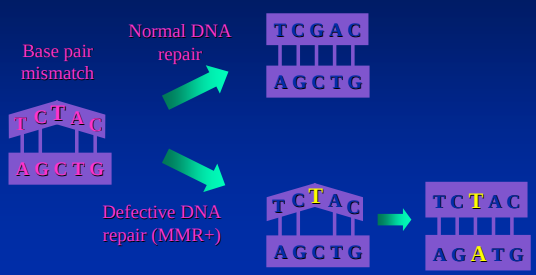


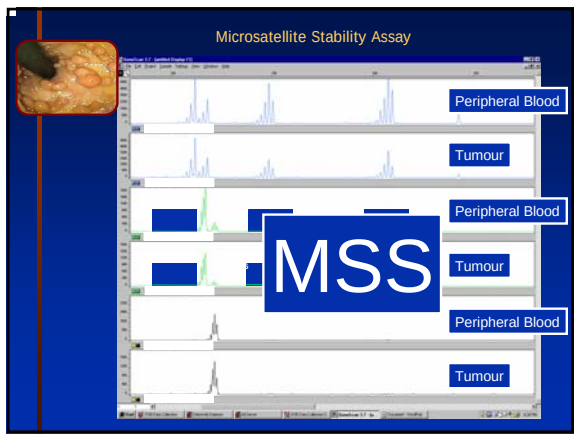
Genetic Heterogeneity in HNPCC

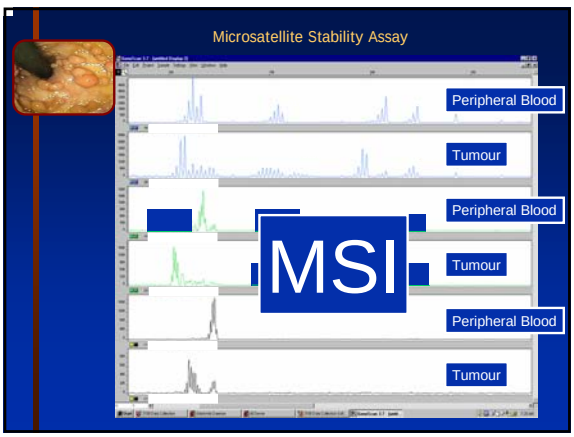


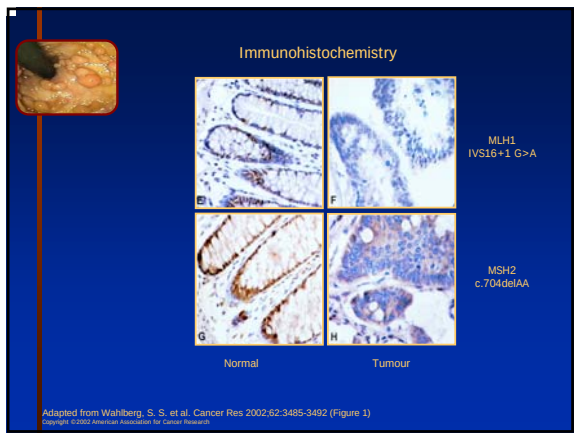
HNPCC is associated with germline mutations in any one of at least five genes: these genes maintain genomic stability
This complicates genetic testing

Microsatellite instabilty: 15% of colon cancers including HNPCC colon cancers

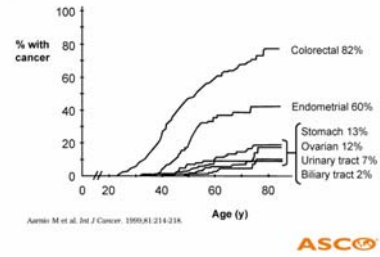




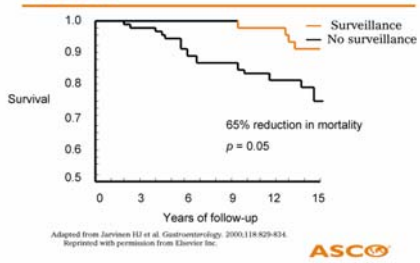




Cancer Risks in HNPCC

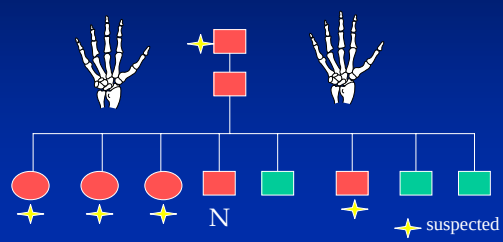


Surveillance Improves HNPCC Survival



Familial diffuse Gastric Cancer

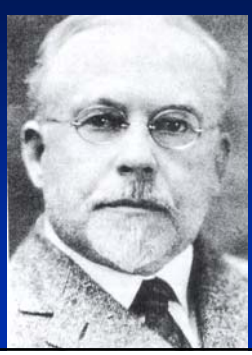
The Buonaparte Experience



Aldred Scott Warthin, M.D., Ph.D. (1866-1931)

The father of clinical cancer genetics

A Renaissance Man -- physician, musician, teacher, writer, editor and, above all, a remarkably creative physician-scientist.



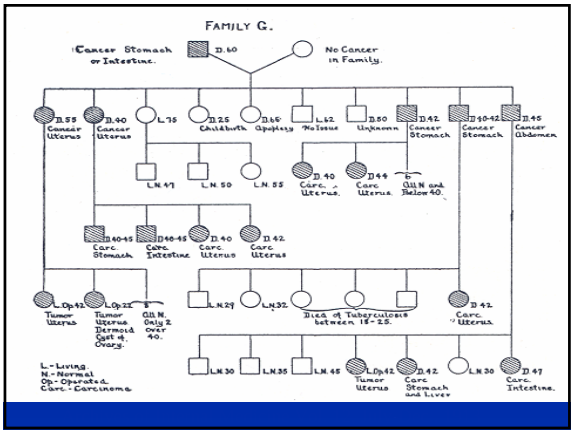
Archives of Internal Medicine 12:546-555, 1913

HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN, 1895-1913 *

ALDRED SCOTT WARTHIN, M.D.
ANN ARBOR, MICH.

The statistical study of carcinoma is regarded by many writers as having been carried as far as it can be profitable; and certainly but little that is new has been gained through this method during the last decade. Nevertheless, its possibilities have not been exhausted; and it is highly



Conclusions

- HDGC is very similar to other cancer susceptibility syndromes
- Mutation testing can identify individuals who could benefit form aggressive management
- Studying rare diseases can teach us things about more more common ones

Many thanks

- Pardeep Kaurah, Janine Senz, Carla Oliveira; David Owen, and Gianpaolo Suriano
- The IGCLC
- B Fernandez, A MacMillan, J Green
- Armelle Troussard, Niki Boyd, J Potter and M Southey
- The families and their care givers

funded by the NCIC, the BC/Yukon chapter of the CBCF and the BC Cancer foundation