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Gastric Cancer: Who to refer for hereditary testing

Dr Savtaj Brar | Mount Sinai Hospital

BC Cancer Surgery Network Fall Update

UNIVERSITY OF TORONTO

Disclosure

I have no financial disclosures

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Outline

I. Identify risk factors for gastric cancer genetic syndromes
II. Summarize the current known gastric cancer genetic syndromes
III. Describe criteria for genetic testing referral

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separating these an ulcer, which penetrated the coats of the stomach, was discovered one inch from the pylorus, sufficient to allow the passage of the little finger. The internal surface of the stomach, to nearly its whole extent, was a mass of cancerous disease, or scirrhous portions, advancing to cancer; this was particularly noticed near the pylorus. The cardiac extremity, for a small space near the termination of the œsophagus, was the only part appearing in a healthy state.

produce such an affection." "It is somewhat remarkable," however, "that he [the Emperor] often said that his father died of scirrhus of the pylorus." His son, of course, died

Case

46 year old female with dyspepsia undergoes OGD after sister is diagnosed with stage 4 gastric cancer at age 48. Father died of stomach cancer in his 50s.

Undergoes total gastrectomy after proximal gastric cancer is found.

In follow up she asks “What should I do about my 2 young daughters?

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Background

- In 2019, it is estimated that 4100 people will be diagnosed with gastric cancer in Canada
- Familial clustering in 10% of cases
- 1-3% of cases are due to hereditary causes
  - Only 40% have an identified genetic mutation

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Familial Syndromes

- Hereditary Diffuse Gastric Cancer (CDH1)
- GAPPS (APC)
- FAP (APC)
- Lynch (MLH1, MSH2, MSH6, PMS2, EPCAM)
- Peutz-Jeghers (STK11)
- Juvenile Polyposis (SMAD4)
- BRCA1/BRCA2 | Li-Fraumeni

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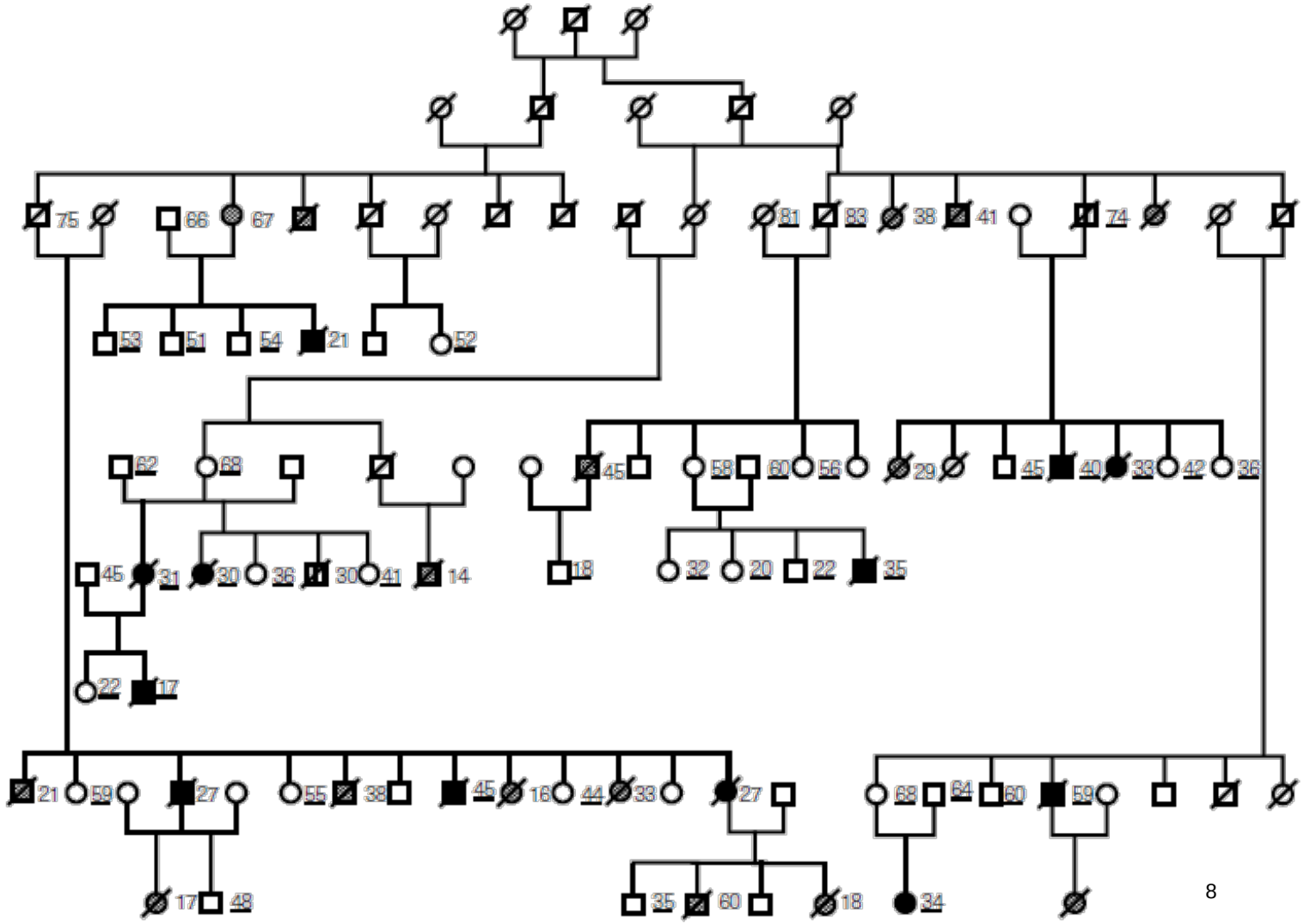
Hereditary Diffuse Gastric Cancer

3 Maori families identified with a high incidence of gastric cancer found to have germline mutations in CDH1



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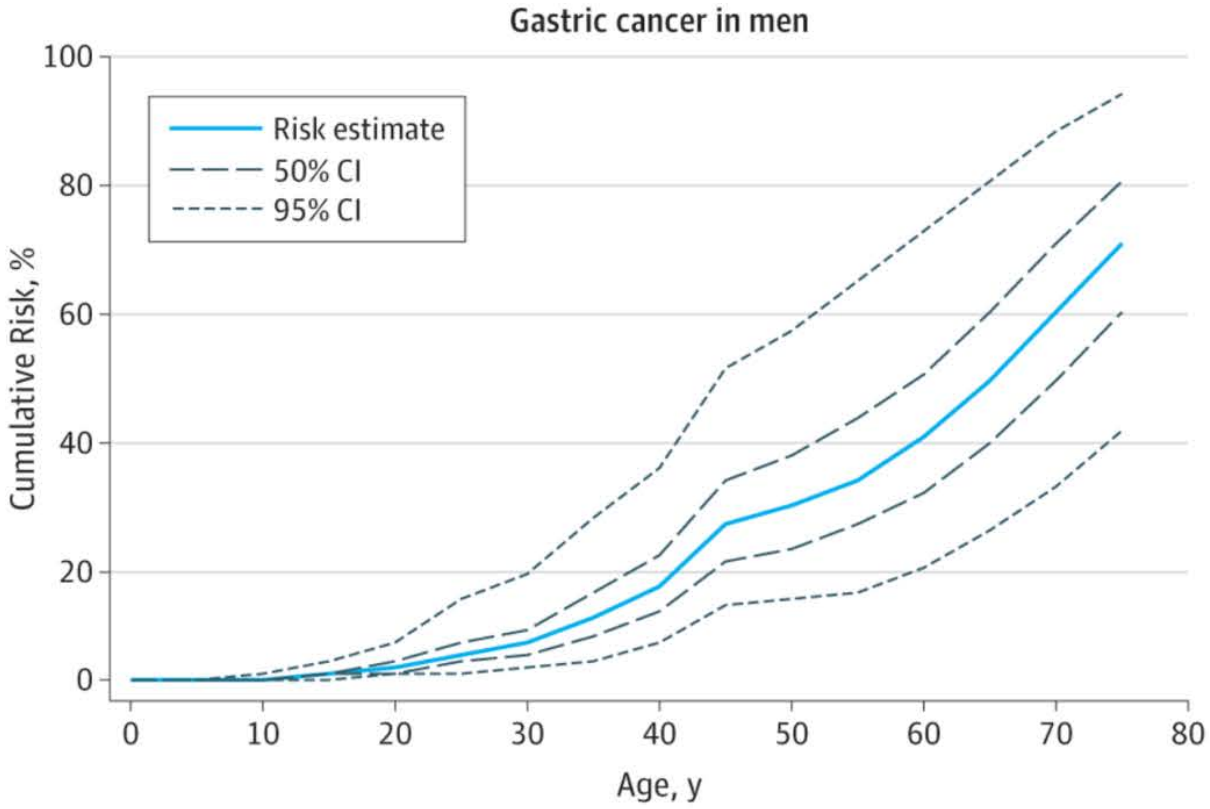
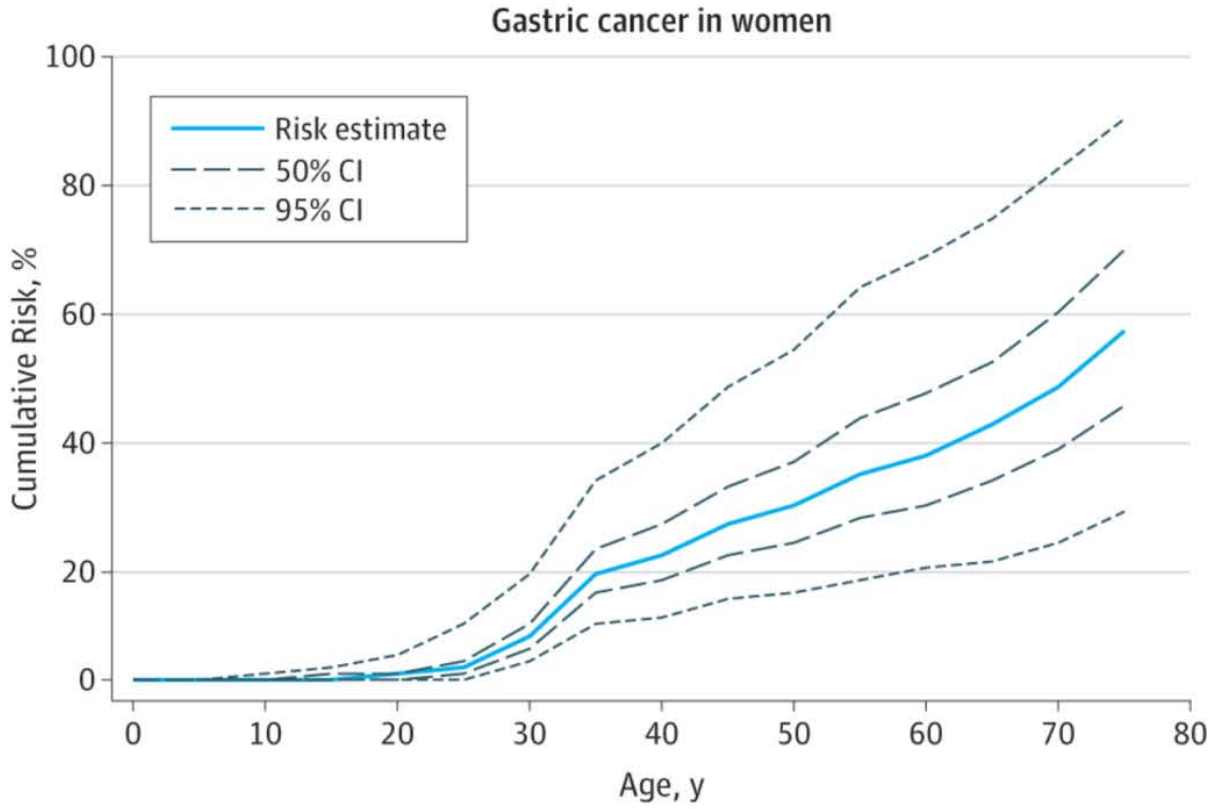
CDH1





lifetime risk of diffuse gastric cancer:

70% in men 50% in women

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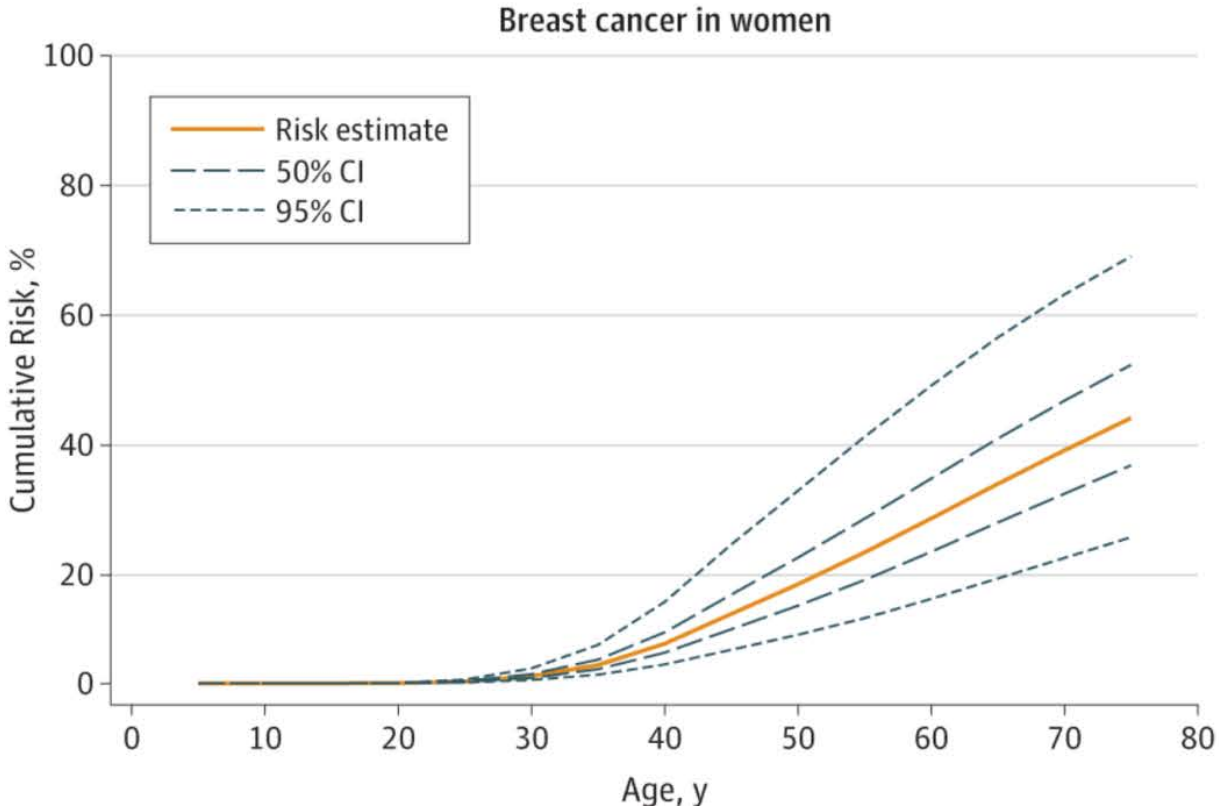
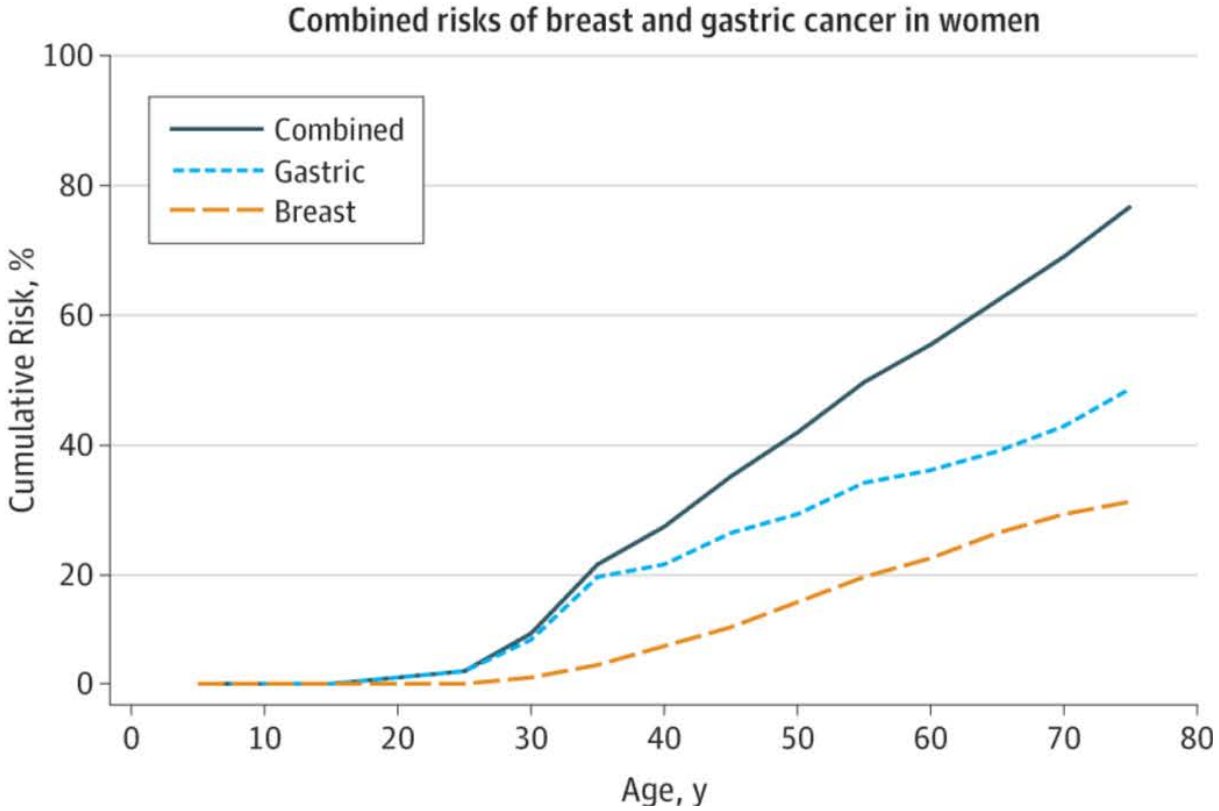
CDH1





40% lifetime risk of lobular breast cancer in women

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CDH1 Testing

1. Two Diffuse gastric cancers in one family, diagnosis at any age
2. Diffuse gastric cancer diagnosed before age 40
3. Personal or family history of diffuse gastric cancer and lobular breast cancer, one < age 50

- At Mount Sinai: also test patients age 40-49

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CDH1 Testing

MSH Familial Gastrointestinal Cancer Registry:

- CDH1 mutations identified in only 11% of patients who met HDGC criteria
- 4 of 14 CDH1 families did not meet testing criteria
  - 3 families *only* presented with breast cancer
  - other was isolated gastric cancer at age 49

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CDH1

- Consensus guidelines recommend that people of age ≥ 20 who harbor a CDH1 mutation undergo prophylactic total gastrectomy (PTG)

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CDH1

- Endoscopy screening (Cambridge protocol)
  - Annual endoscopy with high definition white light scope
  - Repeat insufflation/deflation to assess distensability
  - Mucosal washing with water mixed with mucolytic and anti-foaming agent (simethicone)
  - Biopsy of visible lesions include PALE spots
  - 5 random biopsies from 6 areas: pre-pyloric, antrum, incisura, body, cardia, fundus

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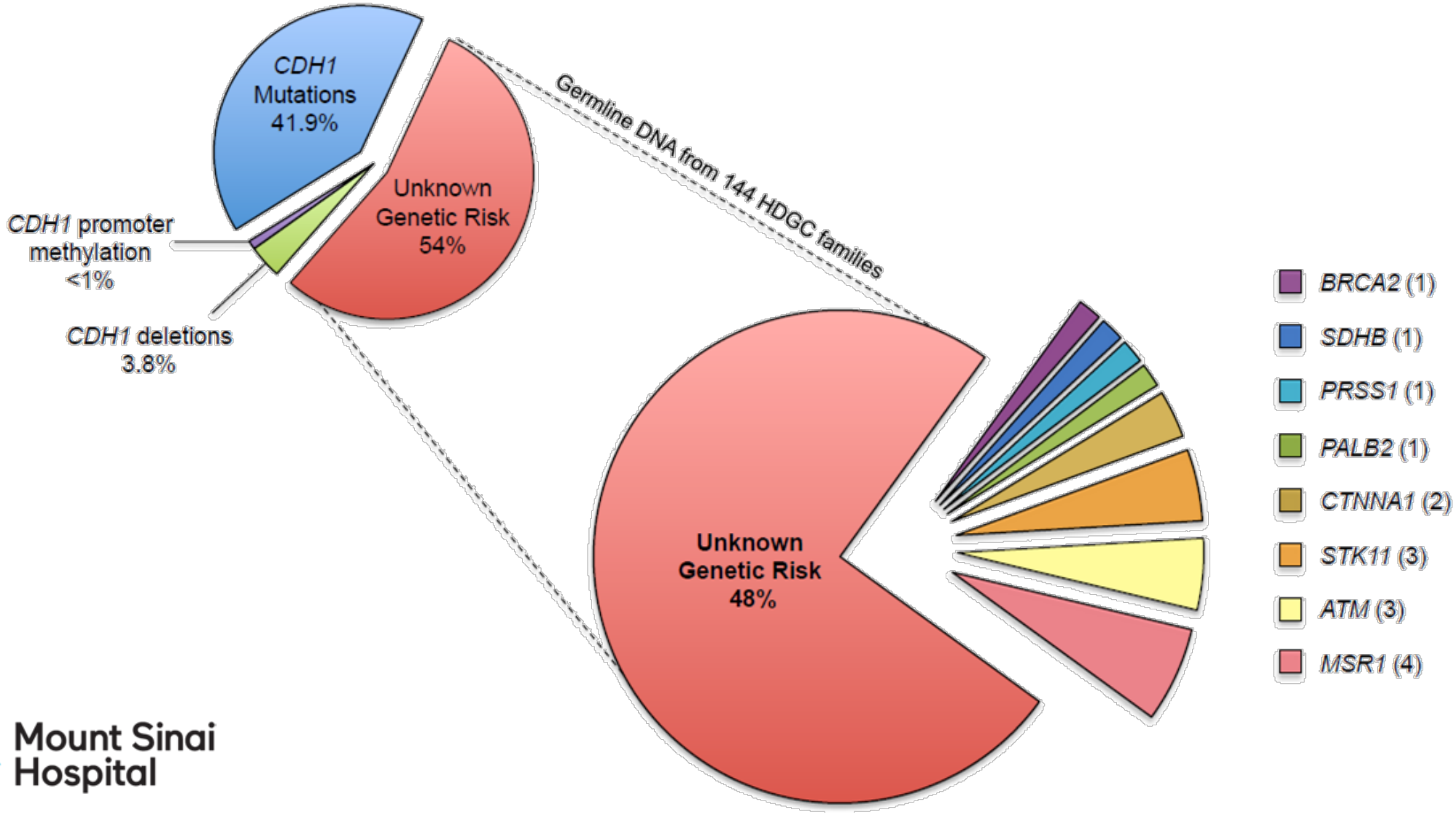
Beyond CDH1



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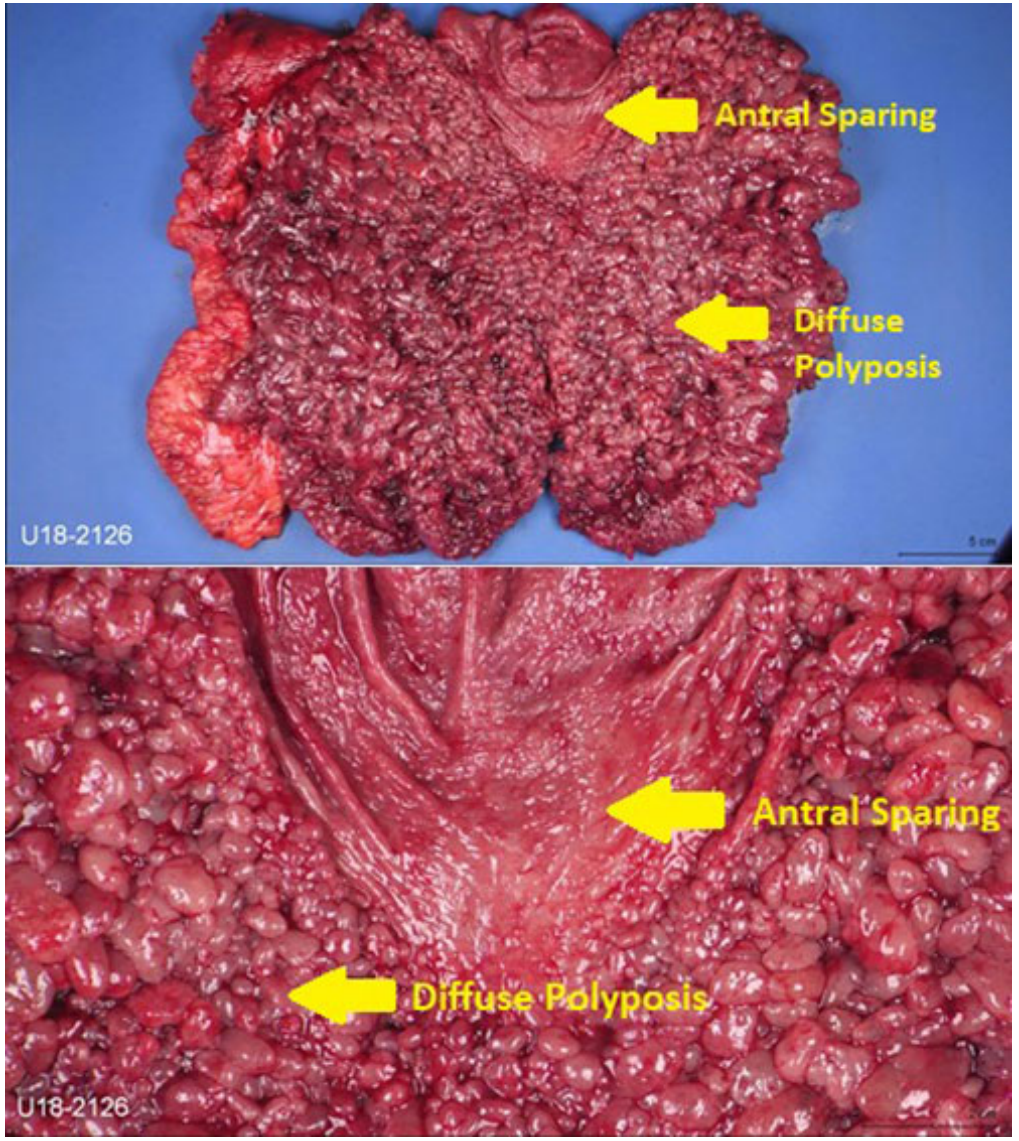
GAPPS

Gastric Adenocarcinoma and Proximal Polyposis Syndrome

Autosomal dominant syndrome with APC gene mutation in promoter IB region



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GAPPS Testing

- Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis
- >100 polyps carpeting the proximal stomach in the index case, or >30 polyps in a first-degree relative of another case
- Predominantly FGP histology, some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma)
- Exclusion of other heritable gastric polyposis syndromes and the use of PPIs

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GAPPS

- Absence of studies on natural history, but endoscopic surveillance has been reported to be suboptimal
  - Patients with GAPPS developing metastatic disease despite no morphologic or histologic changes on surveillance
- Total gastrectomy in GAPPS patients with polyposis is prudent though no guidelines
- Colonoscopy surveillance may be initiated

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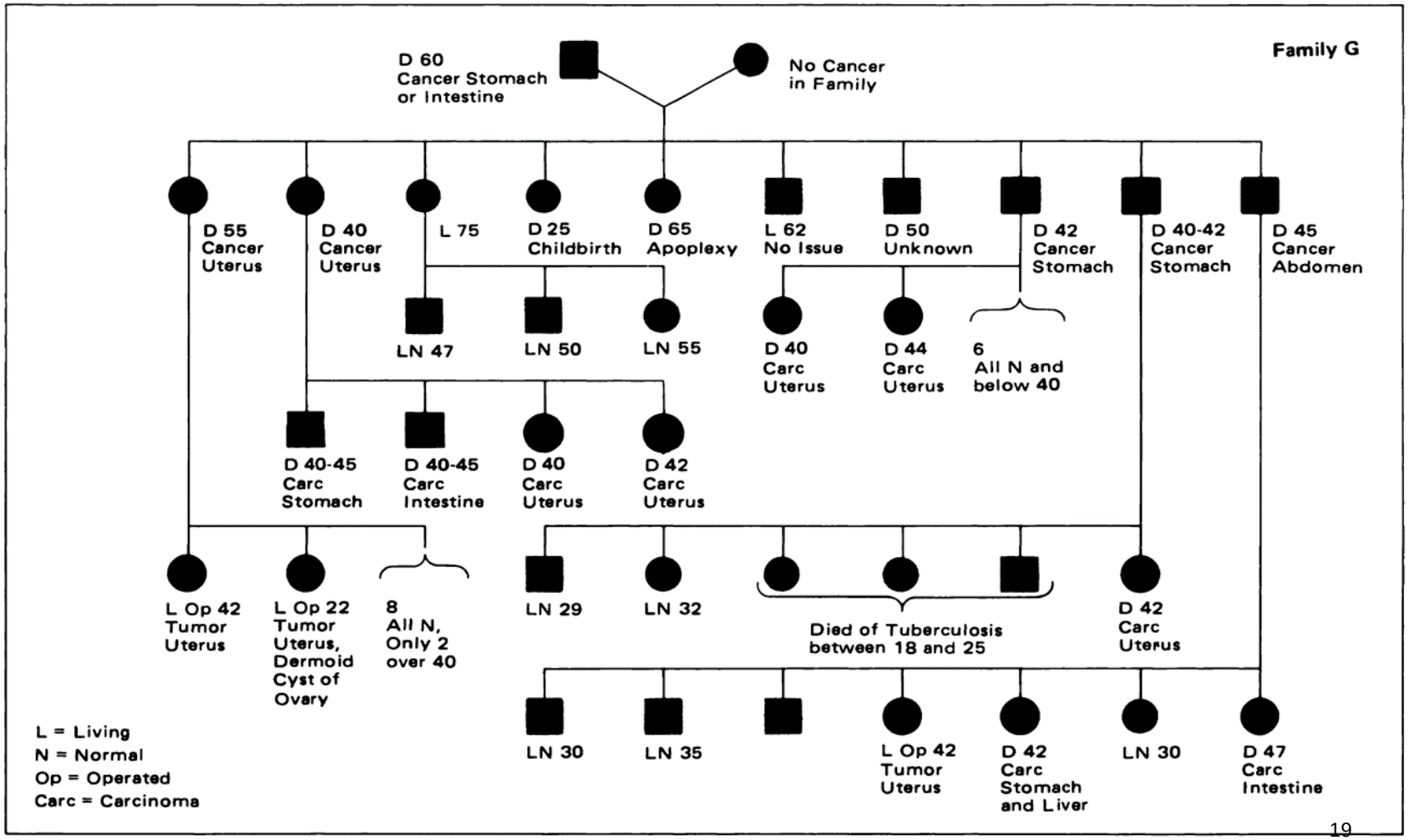
Lynch

Risk of gastric cancer around 7-8% by age 75 (up to 12%)

Intestinal type predominates (75-80%)



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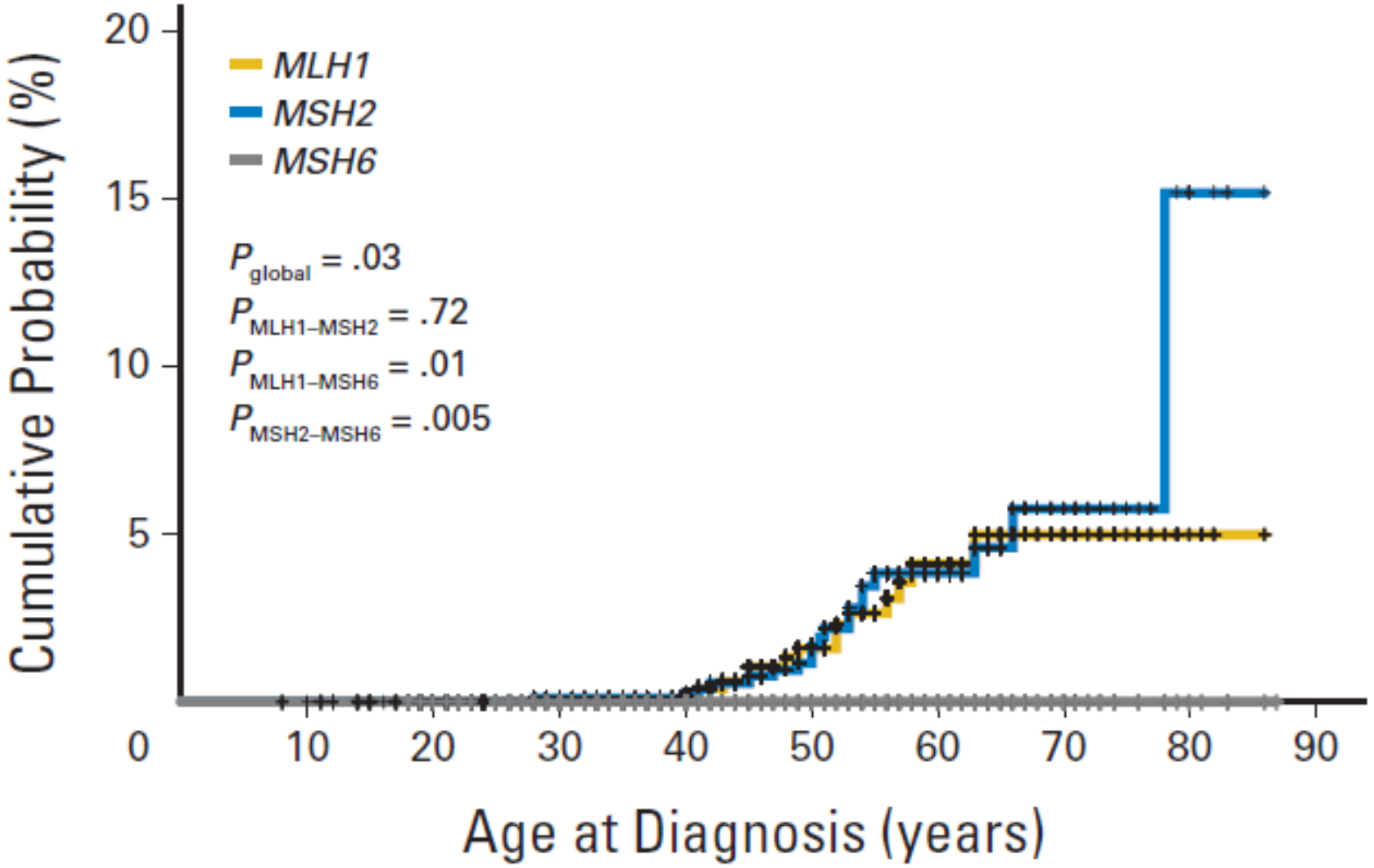
Lynch

MSH2 > MLH1

Male > Female

Risk before age 50 is low, but higher than general population



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Lynch

- Mutation carriers should have baseline OGD at age 30-35
  - H.Pylori testing → eradication
- Consider ongoing surveillance (q1-3 OGD) if:
  - Known risk factors (H Pylori, Intestinal metaplasia, gastric atrophy)
  - Family history
  - Immigration from a high incidence country

* No evidence for surveillance*

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SMAD4

- Juvenile Polyposis syndrome with SMAD4 mutation thought to have ~ 20% risk of gastric cancer
- OGD to start at age 15.
- Repeat annually if polyps are found, and every 2-3 years if no polyps. May decrease frequency after age 35 if no polyps.

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STK11

- Peutz-Jeugers syndrome defined by a germline mutation in STK11 estimated to have ~30% risk of gastric cancer
- Baseline OGD + colonoscopy at age 8
  - If no polyps at baseline, may recommence screening at age 18
  - Repeat endoscopy q 3yrs

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Case

46 year old female undergoes testing for CDH1, not found to have any known mutation or VUS. Panel testing negative for Lynch, STK11, SMAD4, etc.

“What should my two daughters do?”

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Case

- Intensive endoscopic screening in a centre with HDGC expertise for first-degree relatives of patients meeting criteria mentioned above may be recommended
  - Cambridge protocol

- A mutation may be identified in the future

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Thank you !

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Mygutfeeling.ca

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H. Pylori

- Approx 20% population is infected with H.Pylori
  - 10 % develop peptic ulcer disease
  - 3% develop gastric adenocarcinoma
  - <0.1% develop MALT lymphoma

- risk of gastric carcinoma is influenced not only by H. pylori strain and host genetics but also by environment