



Familial Gastric Cancer: Making the Right Decisions at the Right Time

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**NATIONAL
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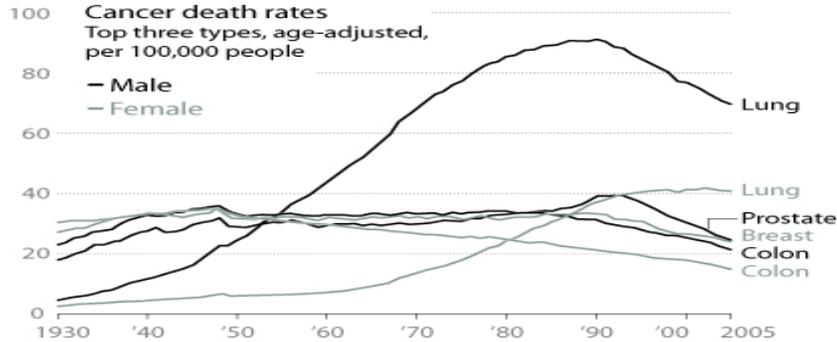
Familial Gastric Cancer: Making the Right Decisions at the Right Time

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Goals:

- Background and making a diagnosis of familial gastric cancer and HDGC
- The implications of the abnormal CDH1 gene in affected families
- Current management of familial gastric cancer

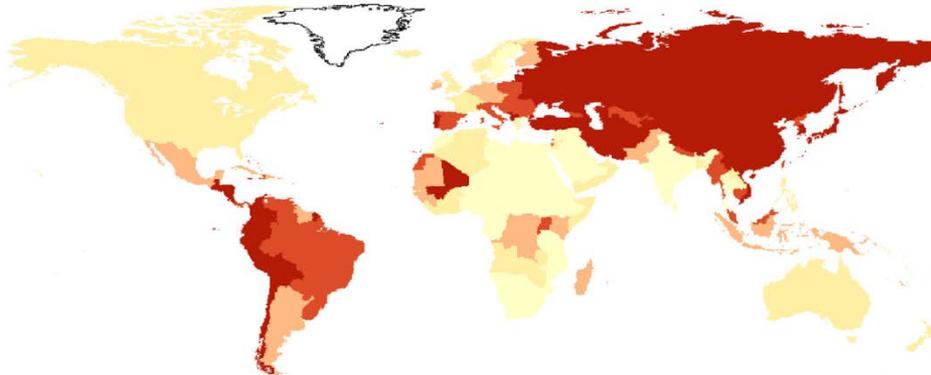
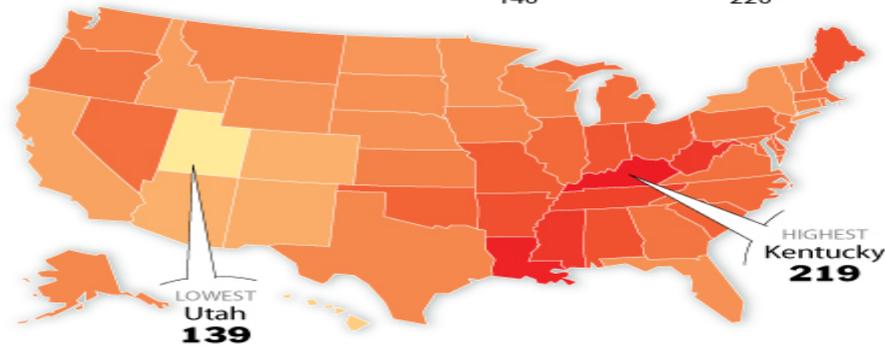
**LUNG CANCER IS STILL THE LEADING
CANCER KILLER OF MEN AND WOMEN ...**



... DEATH RATES ARE SLIGHTLY HIGHER IN THE SOUTH ...

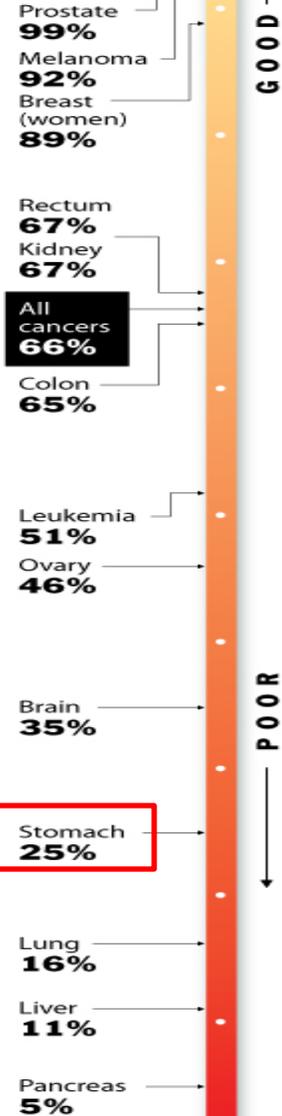
Cancer death rates
Age-adjusted, 2002-06

Per 100,000 people
140 220



< 3.8 < 5.8 < 8.2 < 13.0 < 41.4

**Five-Year
Survival
Rates**
Cancers
diagnosed
1996-2004

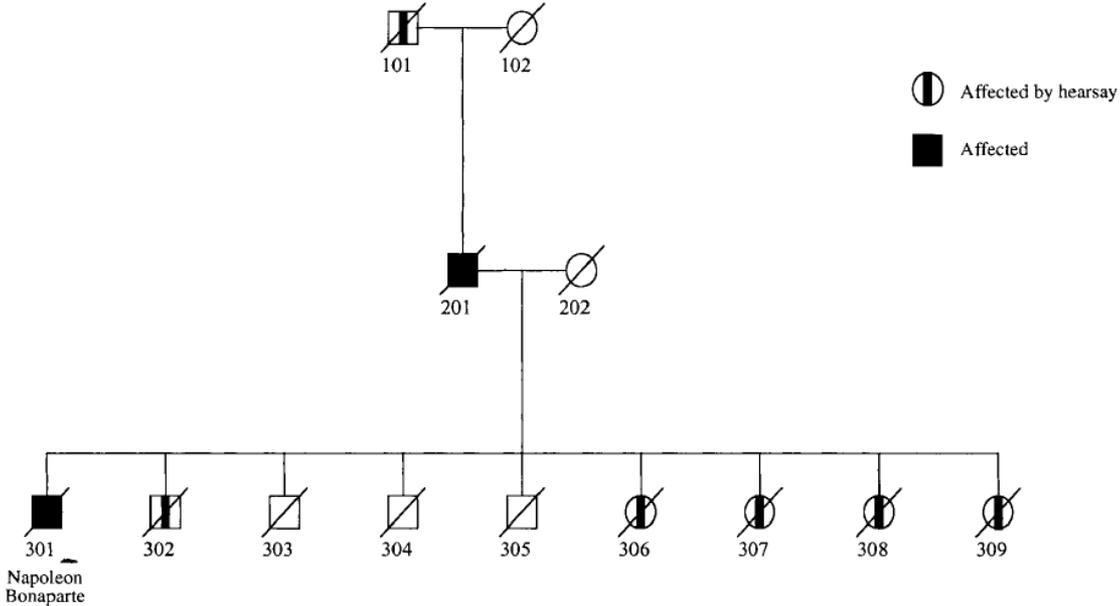


Hereditary GI cancer syndromes WITHOUT polyposis

Syndrome	Gene(s) (chromosomal locus)	Inheritance pattern	Component gastrointestinal neoplasms	Features other than component gastrointestinal neoplasms	
				Malignant neoplasms	Benign neoplasms and other features
CoLoN syndrome ^a	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b <i>PMS2</i> (7p22) ^b	AR	Childhood onset colon cancer; duodenal cancer; colon adenomas	Childhood onset brain tumors; leukemia; lymphoma; endometrial and ovarian cancers ³⁷	Features of neurofibromatosis (café-au- lait spots; neurofibromas)
FAMMM	<i>CDKN2A/p16</i> (9p21) ^b Others	AD	Pancreatic cancer	Melanoma	Dysplastic nevi
Familial Colorectal Cancer Type X	Unknown	Presumed AD	Colon cancer	Families meet Amsterdam I criteria but MSI stable ⁶¹	None
Familial GIST	<i>KIT</i> ^b and <i>PDGFRA</i> (4q12)	AD	GIST	None	<i>KIT</i> : hyperpigmentation; mast cell tumors; dysphagia <i>PDGFRA</i> : large hands
Familial intestinal gastric cancer	Unknown	AD	Intestinal gastric cancer	None ^{62,63}	None
Hereditary diffuse gastric cancer	<i>CDH1</i> (16q22.1) ^b Others?	AD	Diffuse gastric cancer; possible association with signet-ring colon cancer ⁶²⁻⁶⁴	Lobular breast cancer	None
Hereditary pancreatitis	<i>CFTR</i> (7q31) ^b <i>PRSS1</i> (7q35) ^b <i>SPINK1</i> (5q32) ^b	<i>CFTR</i> : AR <i>PRSS1</i> and <i>SPINK1</i> : AD	Pancreatic cancer	None	Pancreatitis
Lynch syndrome (HNPCC)	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b <i>PMS2</i> (7p22) ^b	AD	Colon, gastric, duodenal and/or small bowel, hepatobiliary and pancreatic cancers	Endometrial and ovarian cancers; ureteral and/or renal pelvis cancers; glioblastoma	None
Muir-Torre syndrome ^a	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b	AD	Same as Lynch syndrome	Sebaceous gland carcinomas; extracolonic Lynch syndrome cancers ⁶⁵	Sebaceous gland epitheliomas and adenomas; keratoacanthomas
MEN1	<i>MEN1</i> (11q13) ^b	AD	Gastroenteropancreatic endocrine tumors such as gastrinoma with Zollinger- Ellison syndrome, VIPoma, insulinoma and glucagonoma	Foregut carcinoids, anterior pituitary tumors	Parathyroid adenomas; facial angiofibromas, collagenomas, lipomas, meningiomas and ependymomas
Turcot syndrome ^a	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b <i>PMS2</i> (7p22) ^b	AD	Same as Lynch syndrome	Typically glioblastoma multiforme (other brain tumors reported), extracolonic Lynch syndrome cancers	None

^aLynch syndrome variant. ^bGenes for which there is a commercially available genetic test. ⁶⁶ Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CoLoN, colon tumors and/or leukemia or lymphoma and/or neurofibromatosis features; FAMMM, familial atypical mole-malignant melanoma syndrome; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis cancer syndrome; MEN1, multiple endocrine neoplasia type 1; MSI, microsatellite instability; VIPoma, vasoactive intestinal peptide tumor.

Genetic predisposition to gastric cancer



Bevan S, Houlston RS, *QJM* 1999



E-cadherin germline mutations in familial gastric cancer

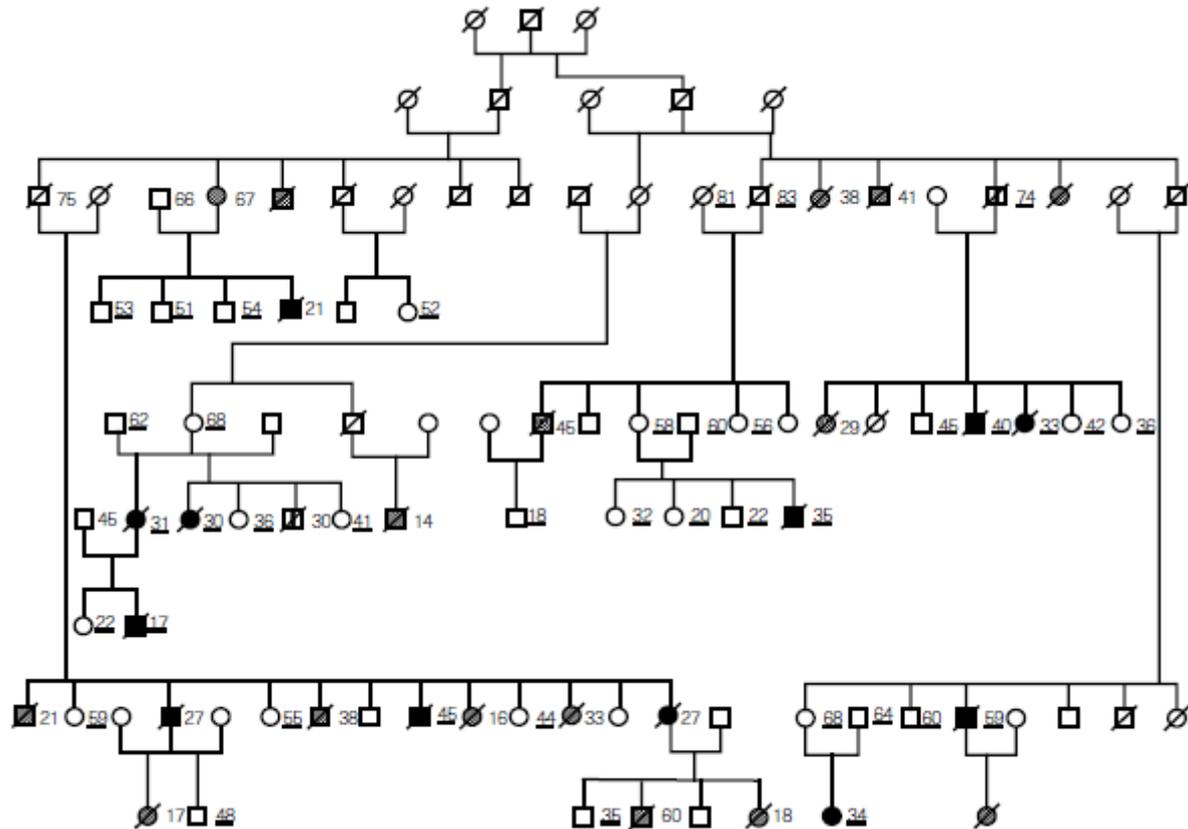
Parry Guilford*, Justin Hopkins*, James Harraway*,
Maybelle McLeod†, Ngahiraka McLeod†,
Pauline Harawira†, Huriana Taite†, Robin Scoular‡,
Andrew Miller§ & Anthony E. Reeve*

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Aotearoa New Zealand



Followed since 1964!

Linkage analysis

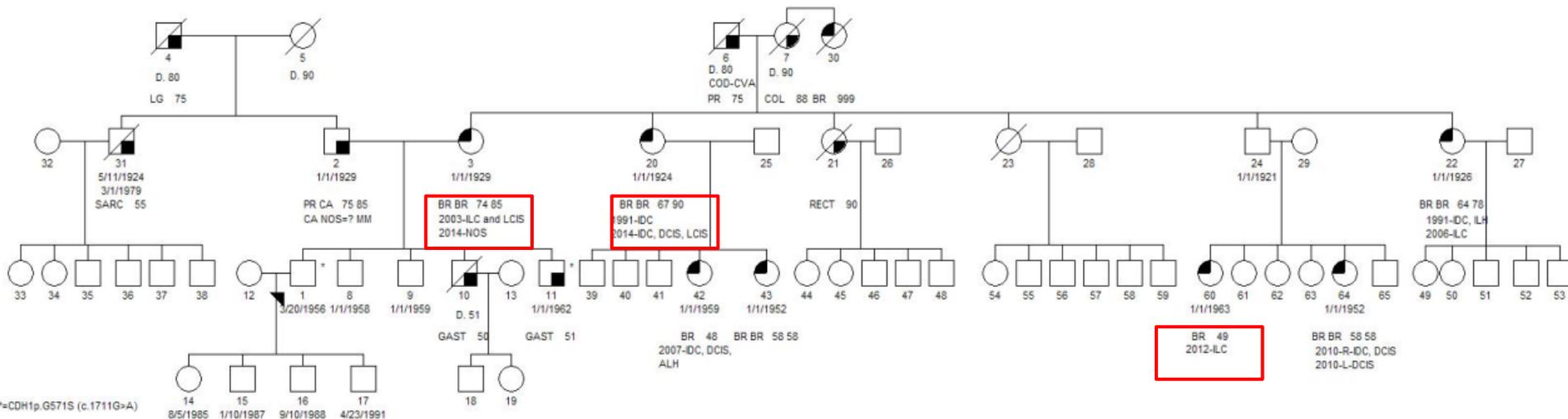
International Gastric Cancer Linkage Consortium (IGCLC)

-within same year of 1998

-criteria to define hereditary diffuse gastric cancer

IGCLC in 2010, extended HDGC guidelines

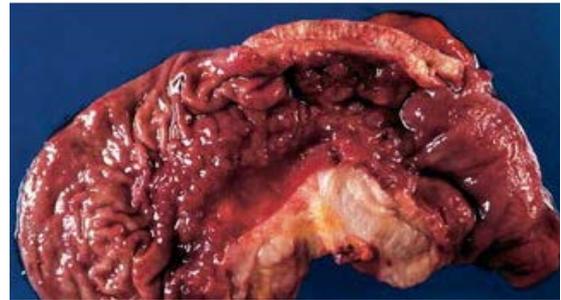
- ✓ two cases of gastric cancer in which one case is histopathologically confirmed as diffuse and younger than 50 years,
- ✓ families with both lobular breast cancer and diffuse gastric cancer, with one diagnosed younger than 50 years, and
- ✓ probands diagnosed with diffuse gastric cancer younger than 40 years, with no family history of gastric cancer.



Lauren classification: Intestinal

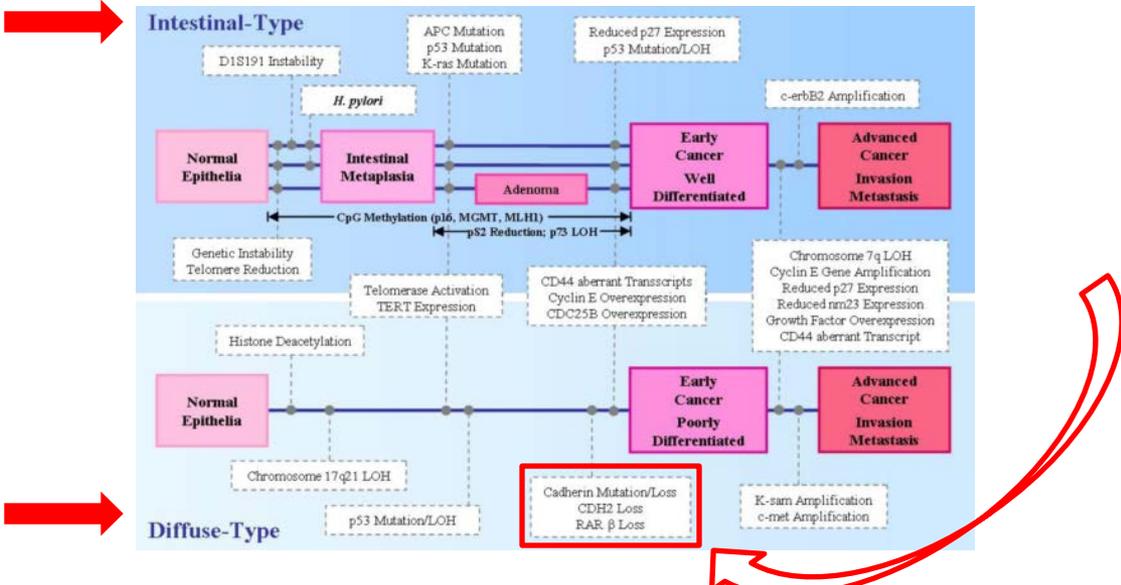
vs

diffuse gastric cancer



1. Poorly differentiated
2. Signet ring cells
3. 'linitis plastica'

Lauren classification: Molecular Implications – two different Diseases

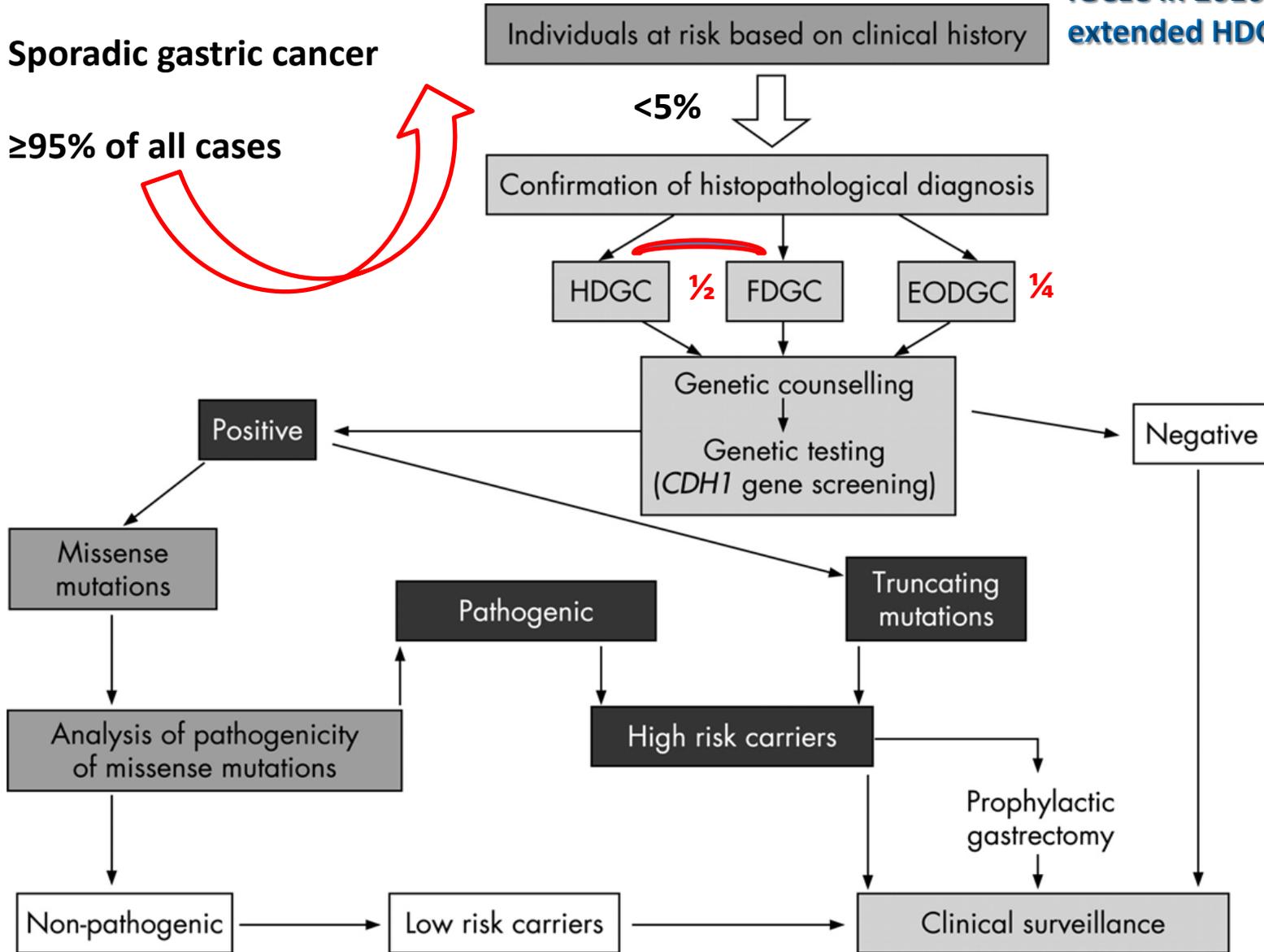


Screening for familial gastric cancer and HDGC

IGCLC in 2010,
extended HDGC guidelines

Sporadic gastric cancer

≥95% of all cases



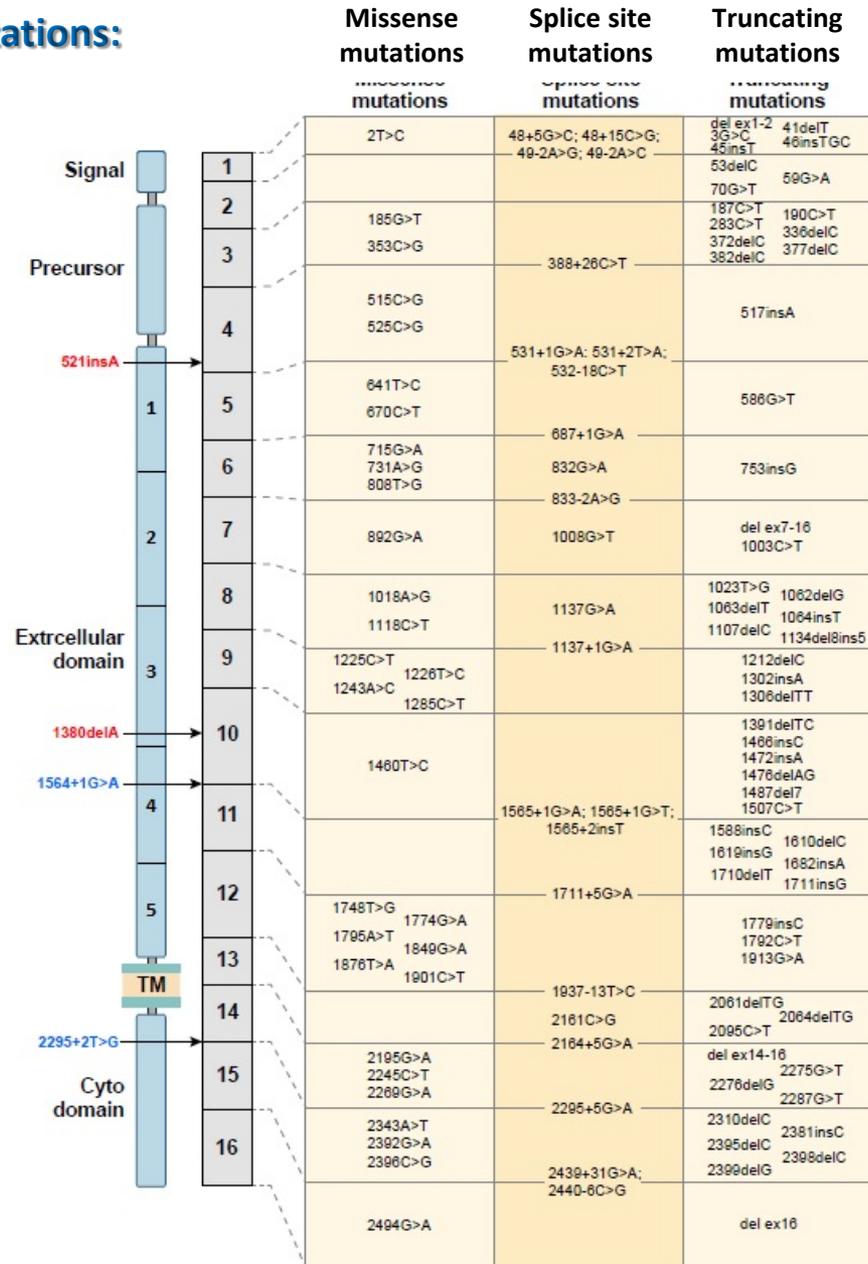
Summary – I:

History of familial gastric cancer

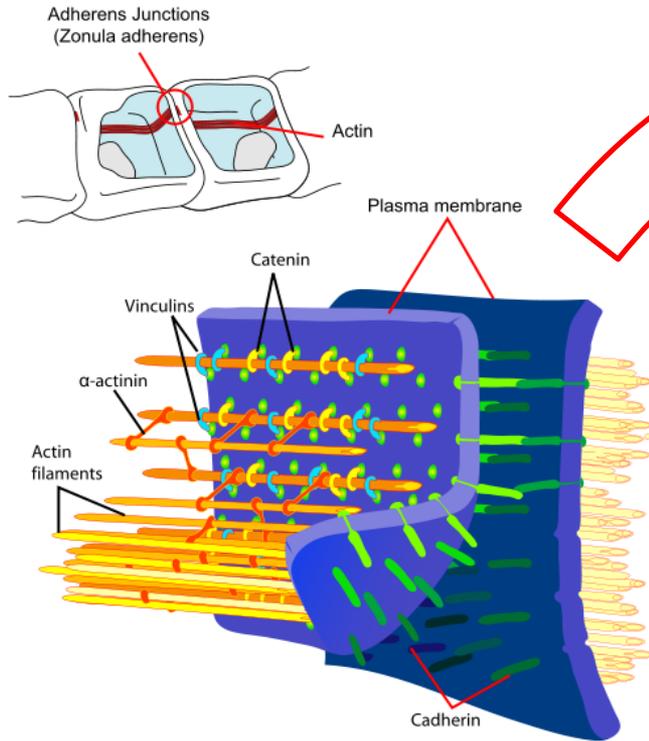
IGCLC Screening guidelines: importance of family history

Not all familial gastric cancer patients harbor CDH1 mutations

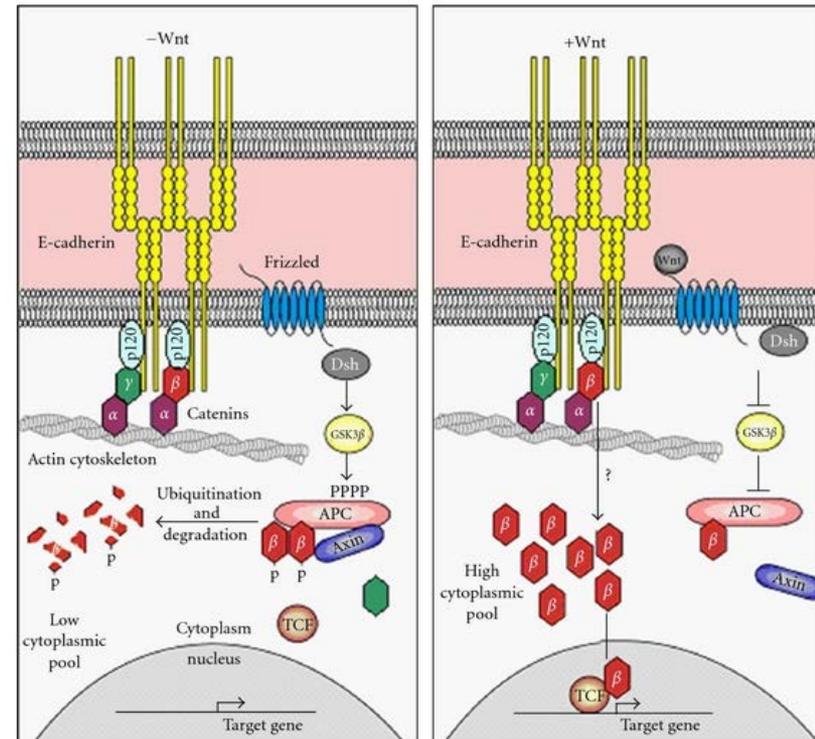
E-cadherin (CDH1) mutations:



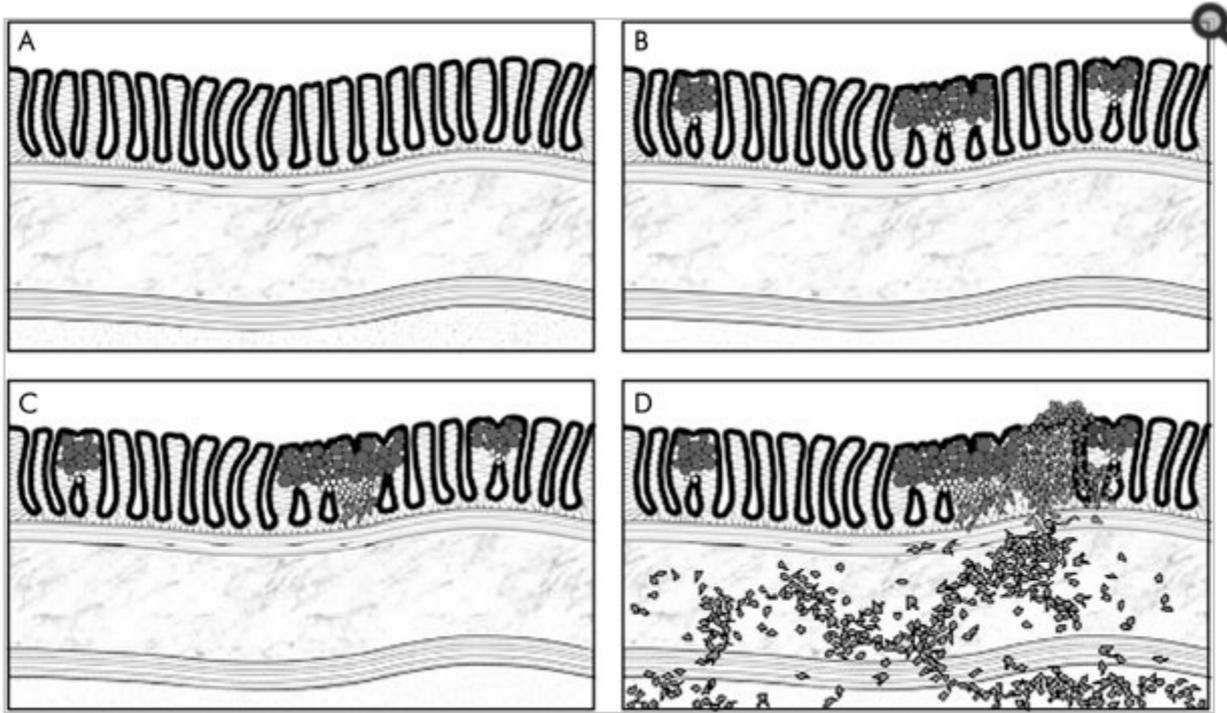
E-cadherin function: regulation cell-cell adhesion



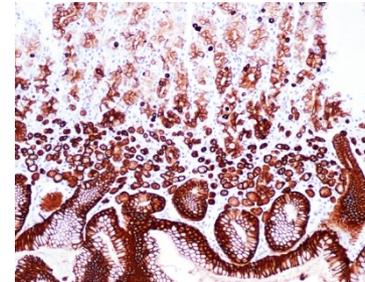
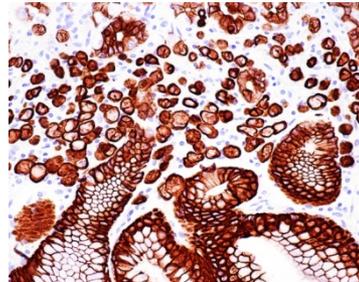
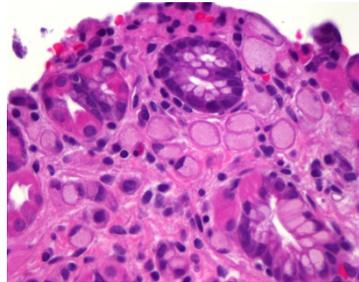
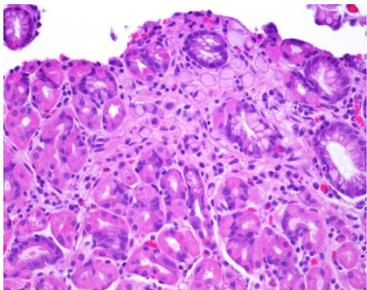
Induction of β -catenin signaling in cells Harboring aberrant CDH1

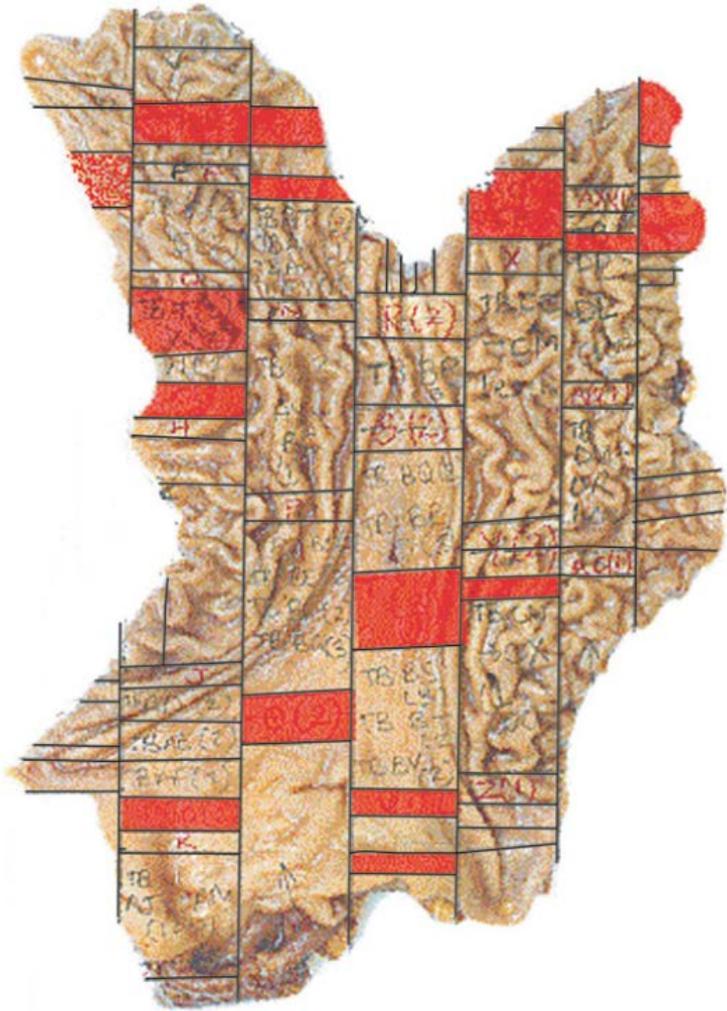


The 'unique' T1a stage in HDGC



Guilford P, *Hereditary Cancer in Clinical Practice*, 2007





Multiple foci of T1a lesions in all prophylactic gastrectomy specimens

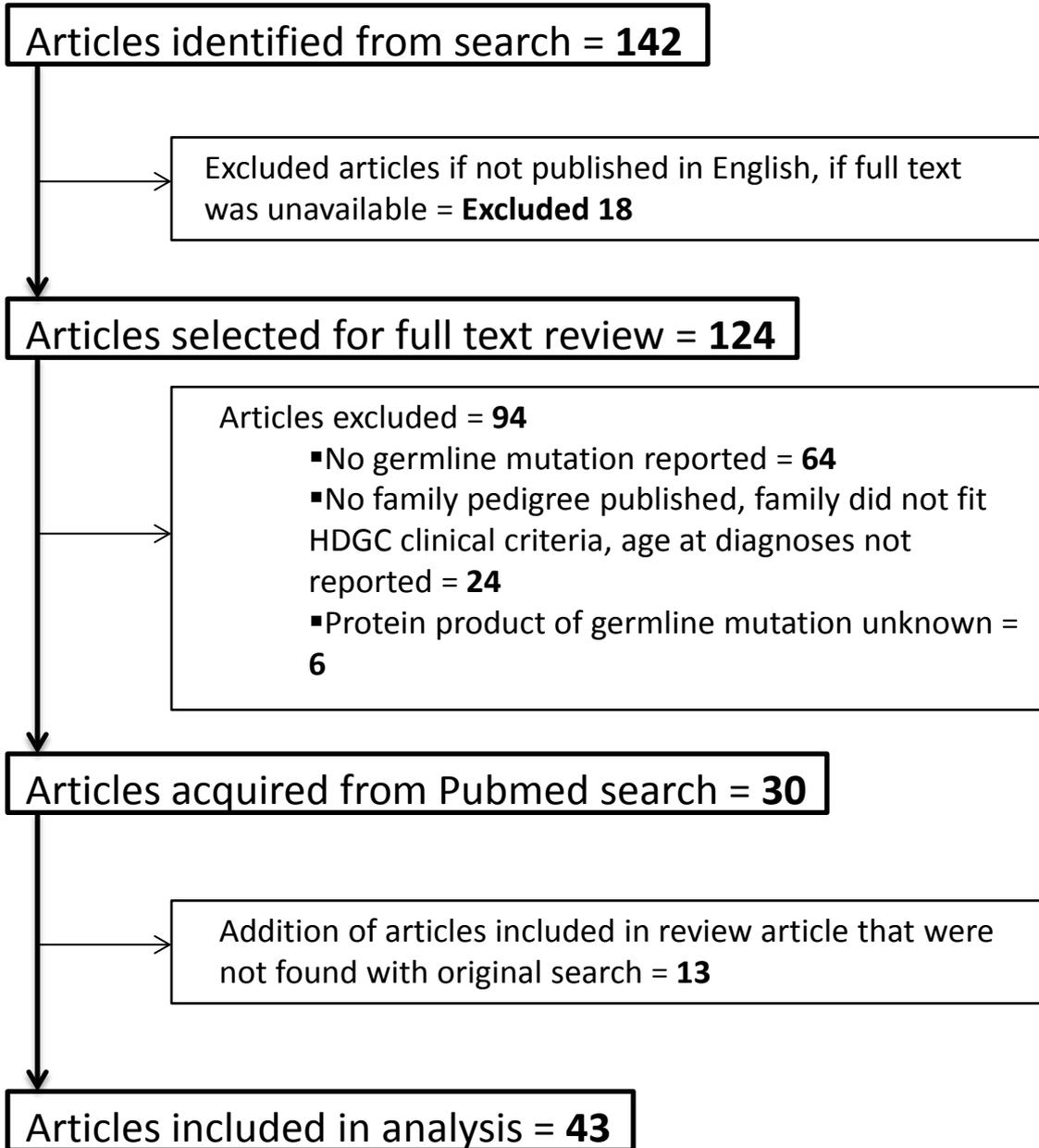
Difficult to detect endoscopically

Long latency - ? when and which lesions will grow

From Fitzgerald RS, Norton J, et al, J Med Genetics, 2010

Do type (mutation vs missense) and/or location of mutation predict clinical course?

Genotype – phenotype relationships in patients with HDGC



Genotype – phenotype associations

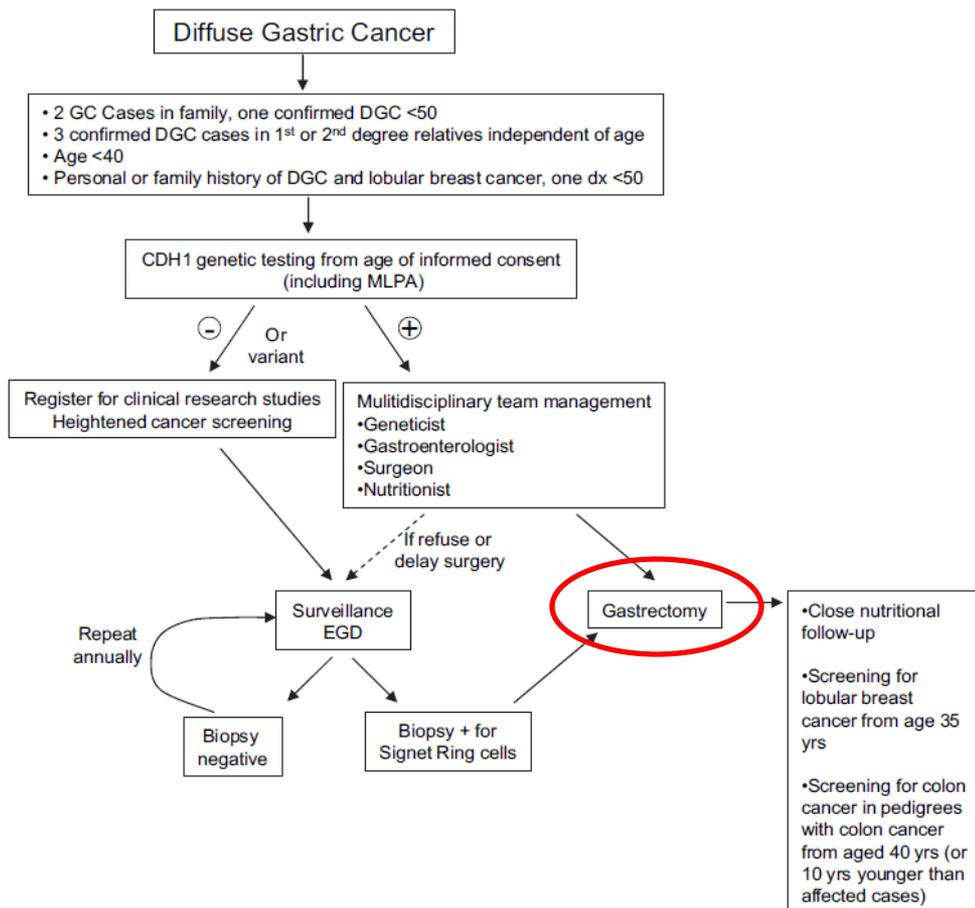
- Family members with missense mutations were
 - more likely to be affected by gastric cancer (increased clinical penetrance (>50%) ($p=0.012$)) and were more likely to
 - come from countries with a high overall risk of gastric cancer ($p=0.0037$ for early vs late truncation, $p=0.0057$ for extracellular vs intracellular truncation).
- Families in which the youngest affected family member was
 - younger than 30 years of age were found to have a higher incidence of other HDGC cancers including lobular breast and colon cancer ($p=0.002$).
- No statistically significant association between type of mutation
 - Age of presentation
 - Presence of other HDGC syndrome cancers

Summary - II:

The function of the CDH1 gene (tumor suppressor)

The unique T1a stage, incl. the 'latency'

Novel genotype-phenotype studies might help
select patients for better for surveillance and
therapy



Carriers of CDH1 mutations have an approximately 70% lifetime risk of developing diffuse gastric cancer

Women with CDH1 mutations have an additional 20-40% risk of developing lobular breast cancer (ILC)

Carriers of CDH1 mutations also harbor a 5-10% risk of developing colon cancer

-> what about the families no CDH1 mutation is detected?

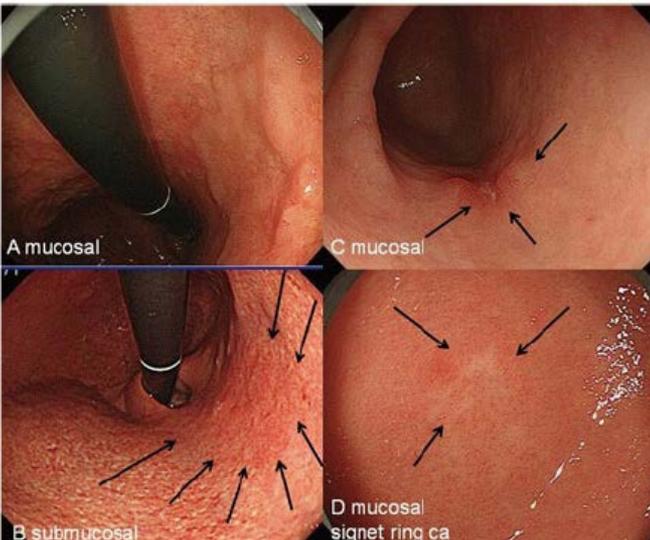
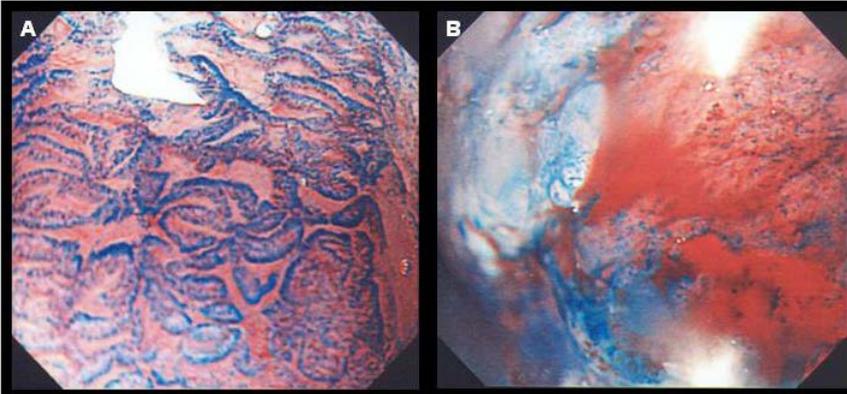
Prophylactic total gastrectomy for HDGC:

Alternative?

Usually with methylene blue and congo red

When?

New genotype-phenotype correlations might help



Able to pick up $\geq 70\%$ of lesions

At least once per year

Highly operator-dependent

Cases of missed cancers reported

Approach to ILC:

- LBC is less likely to form calcifications or discrete mass lesions -> mammography less effective, MRI breast recommended
- Breast surveillance recommended to begin at age 25
- LBCs are estrogen-receptor positive -> tamoxifen is an option for chemoprevention
- Prophylactic bilateral mastectomy has been performed but its role remains undefined

Approach to increased risk of colon cancer:

- Colorectal cancer screening should begin five to 10 years earlier than the earliest diagnosis of colorectal cancer in the family or by age 50, whichever is sooner.

In general:

- Multiple modalities for surveillance have been used, but all have proven ineffective for early detection of HDGC

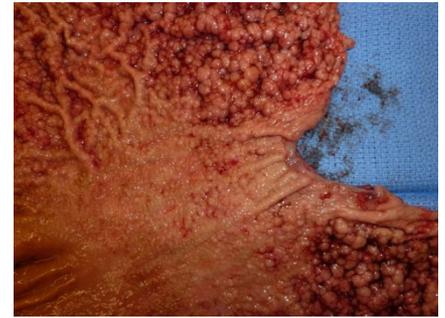
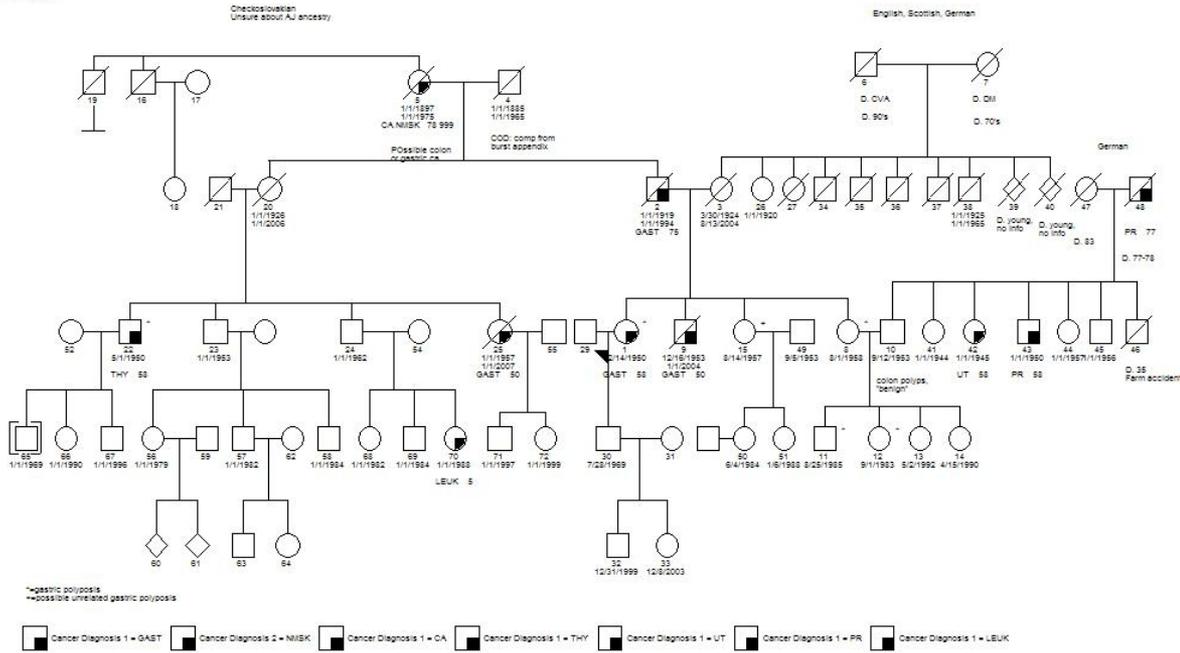
Role of prophylactic gastrectomy:

- Offered to all carriers of inactivating CDH1 mutations
- It is critical that a total gastrectomy needs to be performed
- Prophylactic gastrectomy specimens are typically found to harbor early foci of DGC
- Close collaboration with nutritionist and PCP important

Summary – III:

- Prophylactic gastrectomy is the most effective 'curative' option to prevent gastric cancer
- Women harboring germline CDH1 mutation should be followed at a breast center and have early breast surveillance which includes MRIs
- Chromoendoscopy can – at the moment – not be recommended as an effective screening strategy

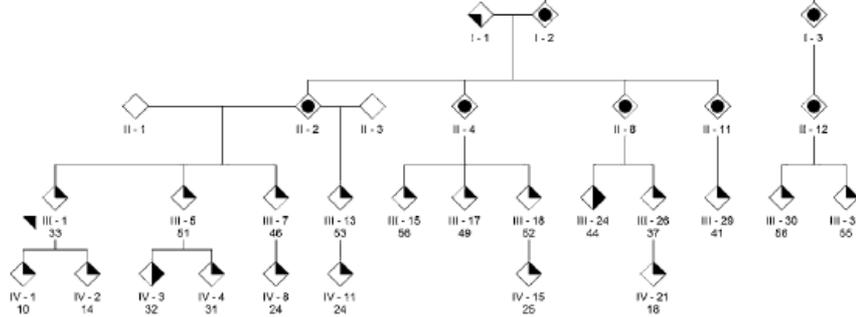
What about the other familial gastric cancer patients not harboring CDH1 mutations?



Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome

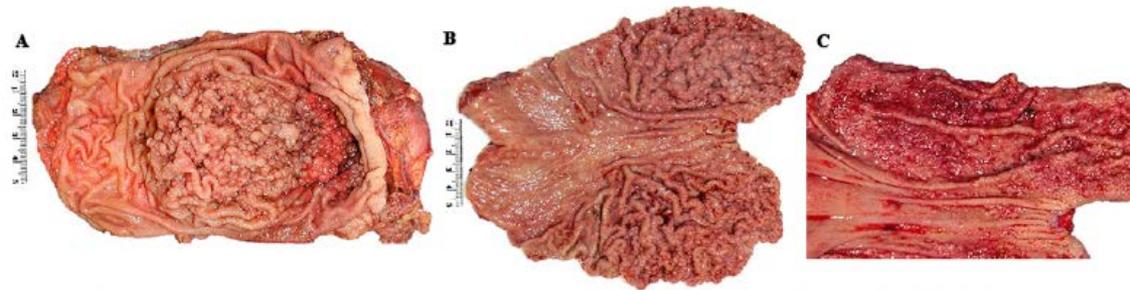
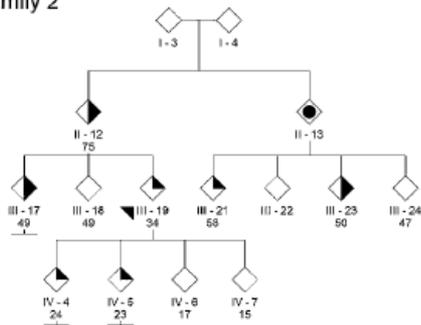
D L Worthley,¹ K D Phillips,² N Wayne,³ K A Schrader,⁴ S Healey,⁵ P Kaurah,⁴ A Shulkes,⁶ F Grimpen,⁷ A Clouston,⁷ D Moore,⁸ D Cullen,⁹ D Ormonde,⁹ D Mounkley,¹⁰ X Wen,¹¹ N Lindor,¹² F Carneiro,¹¹ D G Huntsman,⁴ G Chenevix-Trench,⁵ G K Suthers^{2,13}

Family 1

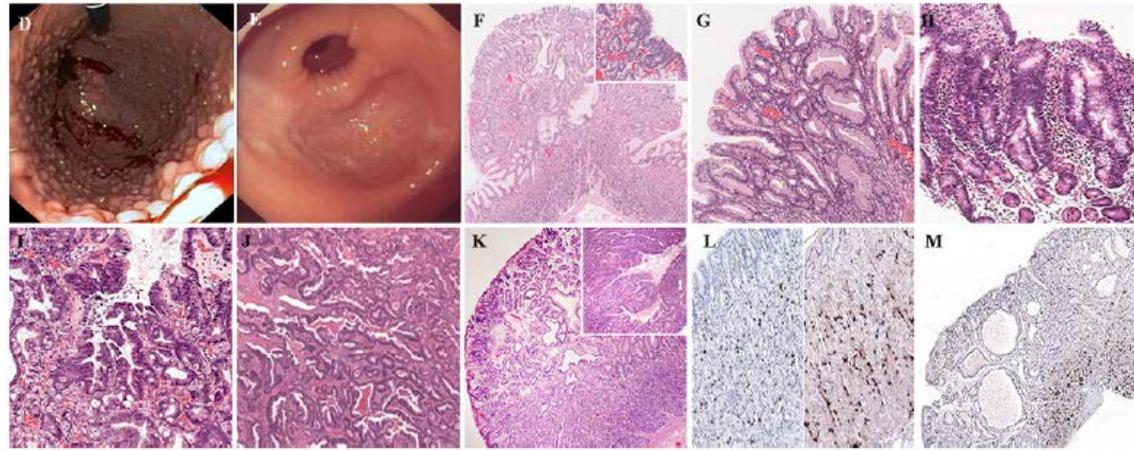
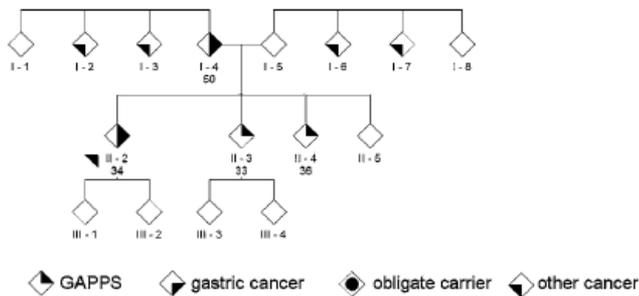


Worthley DL, *Gut*, 2012

Family 2



Family 3



Considering the high lethality of metastatic gastric cancer and the unknown natural history of CDH1 mutation negative familial gastric cancer

- In the absence of a marker (e.g. CDH1 mutation status in HDGC) there is an increased role of endoscopic surveillance**
- Patients with endoscopic abnormalities and a positive family history of familial gastric cancer should be offered total gastrectomy**

-A 'specific' role for nursing in this disease:

Rare disease, to date >100 families well described

To fill the void of information on the natural history (improved family history, identifying patients AT RISK which have not been screened yet)

As per:

Hereditary diffuse gastric cancer: lifesaving total gastrectomy for CDH1 mutation carriers.

Lynch HT, Lynch JF.

J Med Genet. 2010 Jul; 47(7):433-5.

Thank you for the invitation!

Ina Chen

Joal D. Beane

Seth Steinberg

And our patients . . .

Questions?