

Hereditary Diffuse Gastric Cancer

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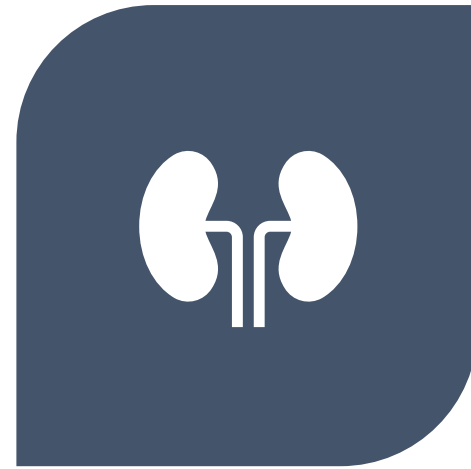
Overview

- Getting on the same page
 - Genetics
 - Classification systems for gastric cancers
- Quick history of CDH1
- Treatment
 - Rationale
 - Special circumstances
 - Life after gastrectomy
 - Weight
 - Quality of life

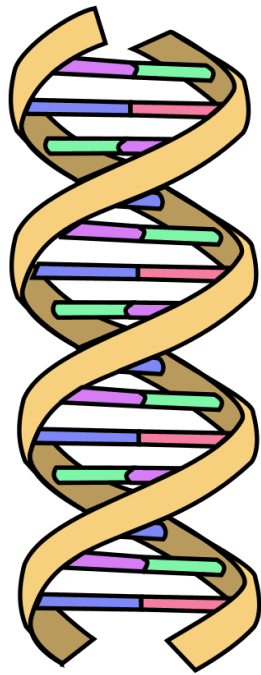
Remember High School Biology?



GENETICS

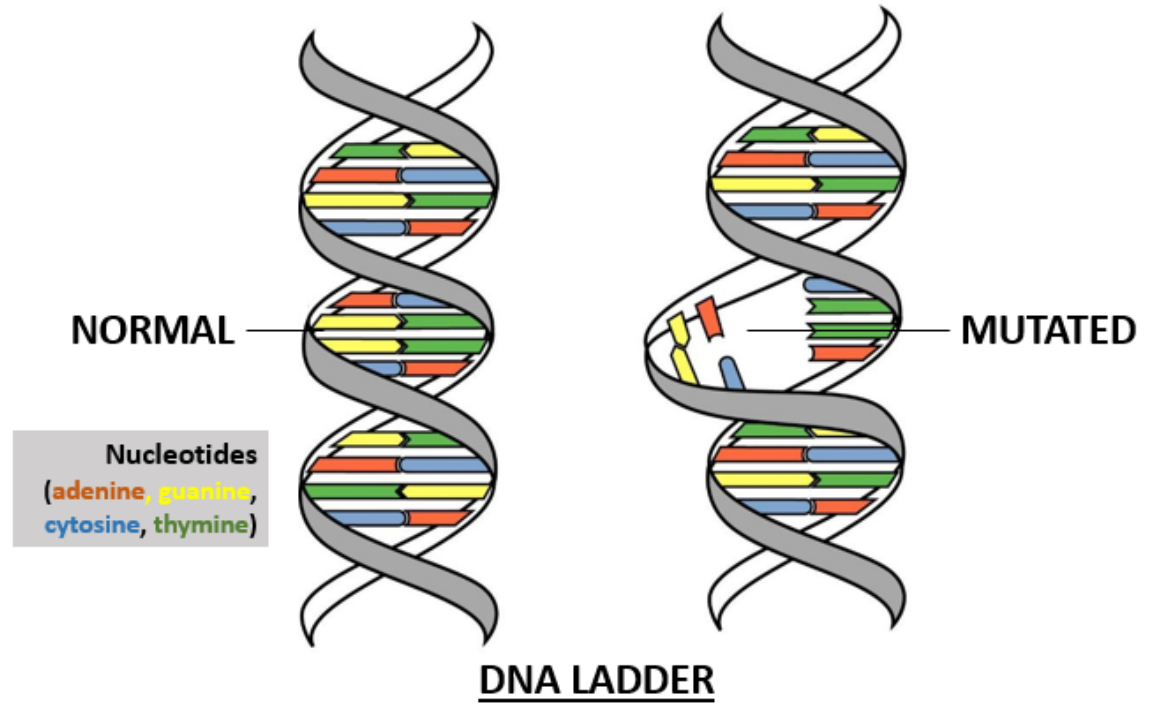


ANATOMY



DNA

-  = Adenine
-  = Thymine
-  = Cytosine
-  = Guanine
-  = Phosphate backbone



Genetics

Working Elements Cell → Proteins



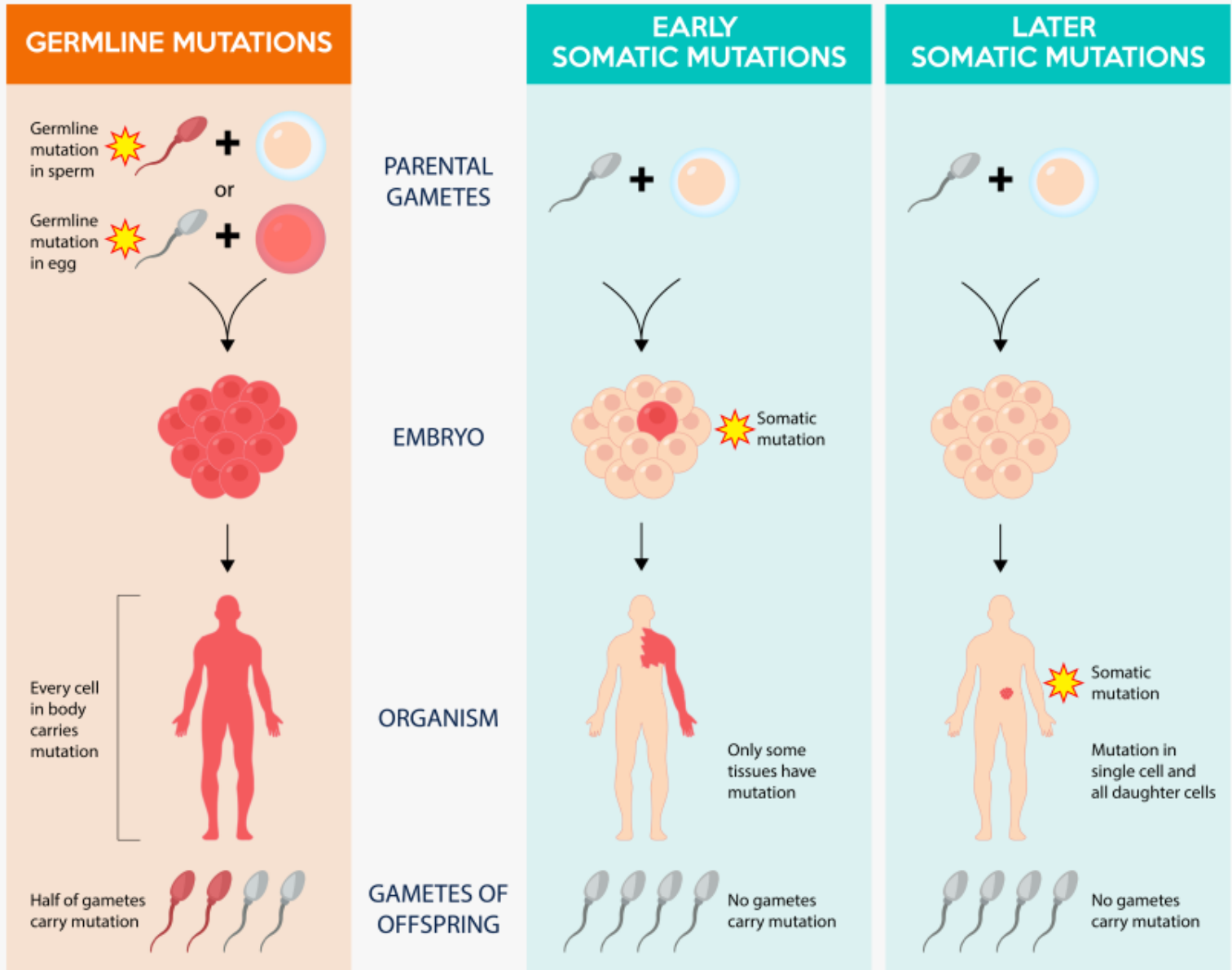
MUTATED

Nonfunctional Protein

Dysfunctional Protein

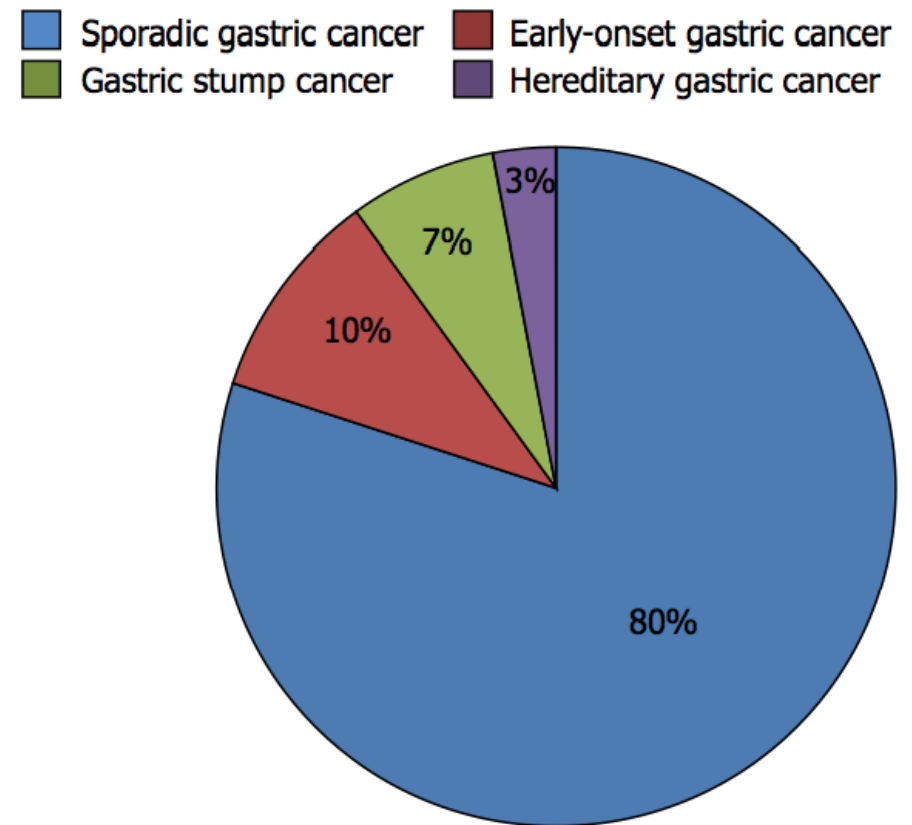
Absent Protein

Genetics

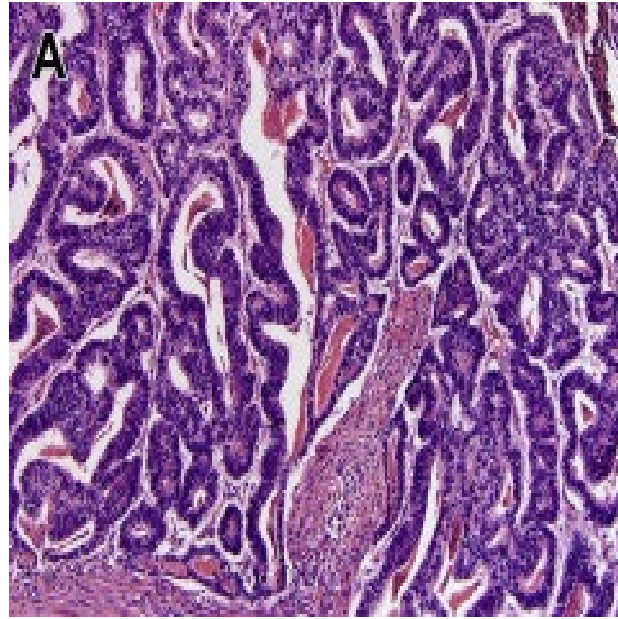


Early Onset Gastric Cancers

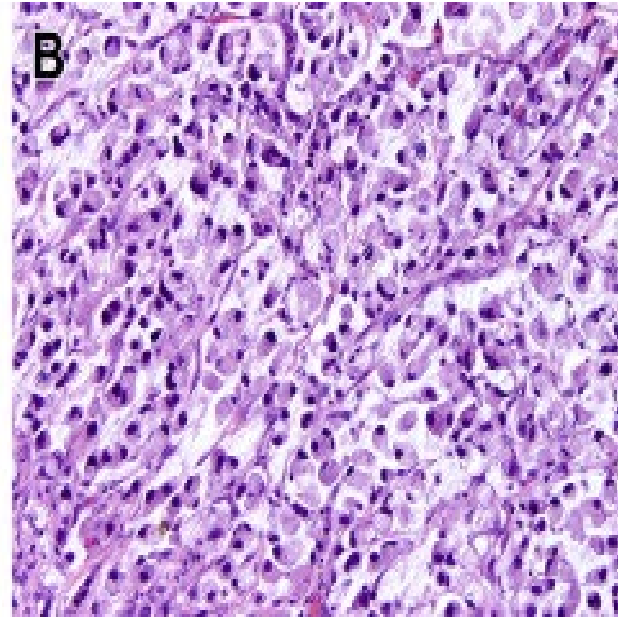
- 10% of gastric cancers are aggregated within families
- 1-3% are hereditary
 - Hereditary **Diffuse** Gastric Cancer (CDH1 > CTNNA)
 - Familial **Intestinal** Gastric Cancer
 - Polyp associated syndromes



Histology – Lauren Classification

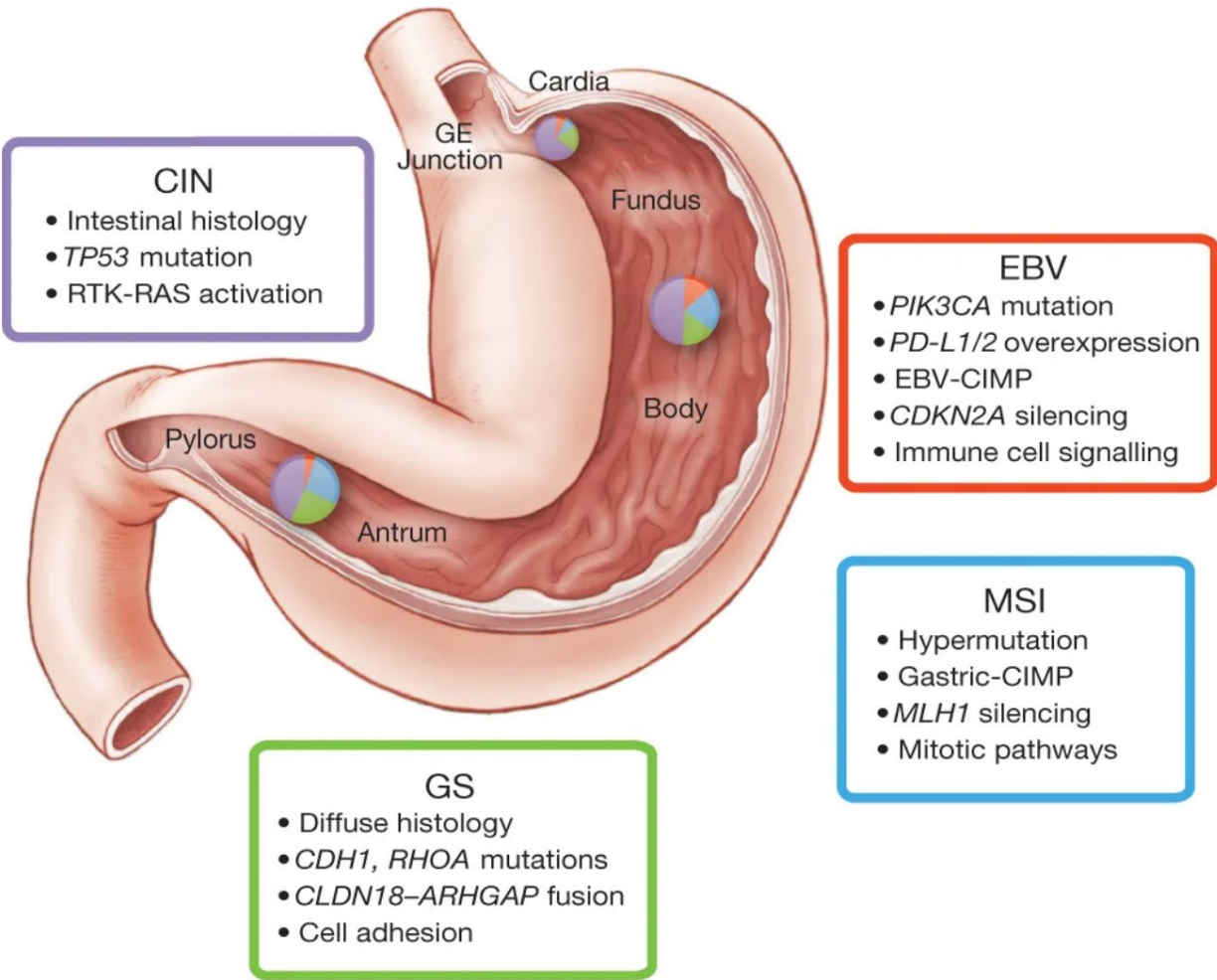
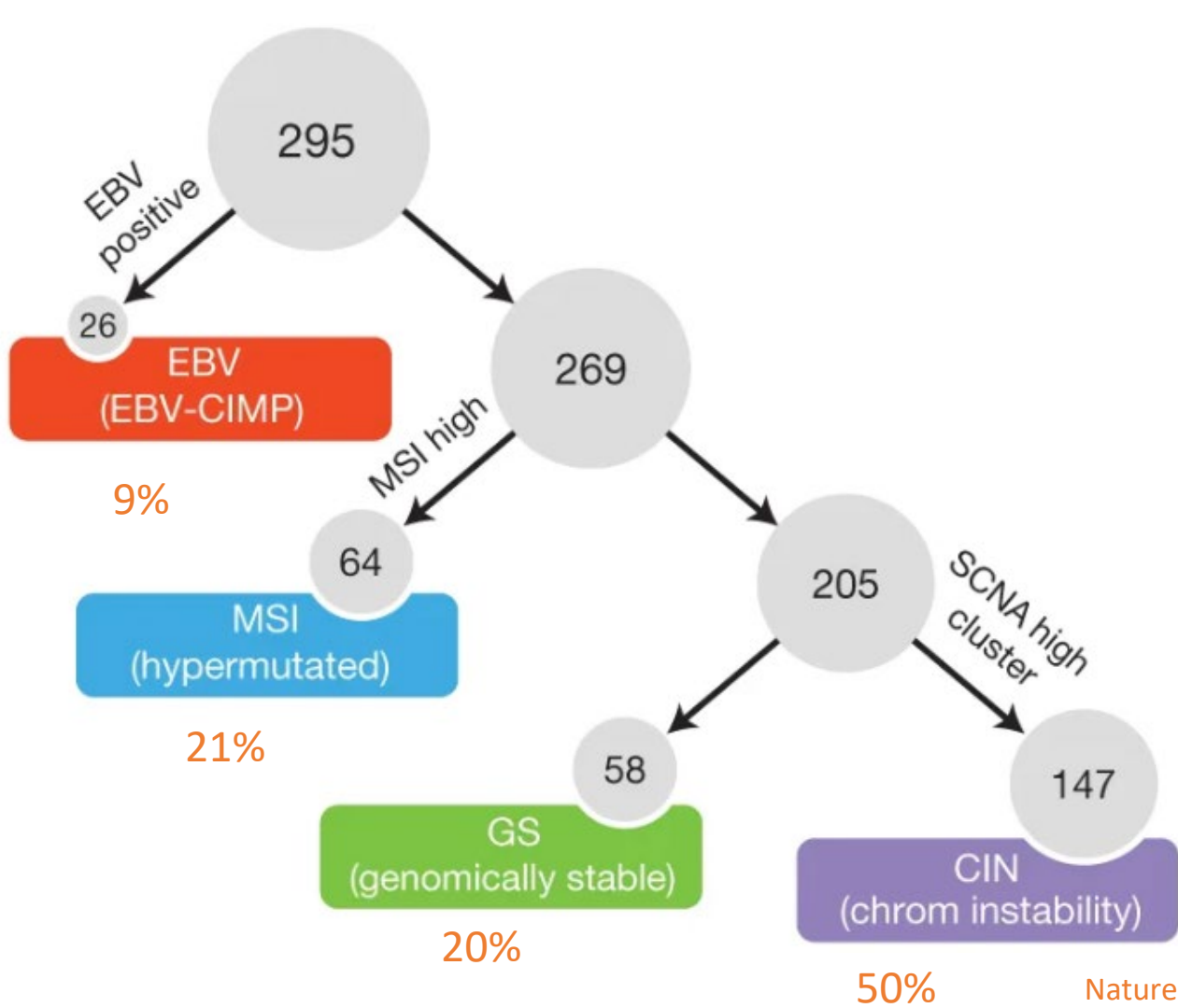


Intestinal



Diffuse

Comprehensive molecular characterization of gastric adenocarcinoma



Nature “Comprehensive molecular characterization of gastric adenocarcinoma”

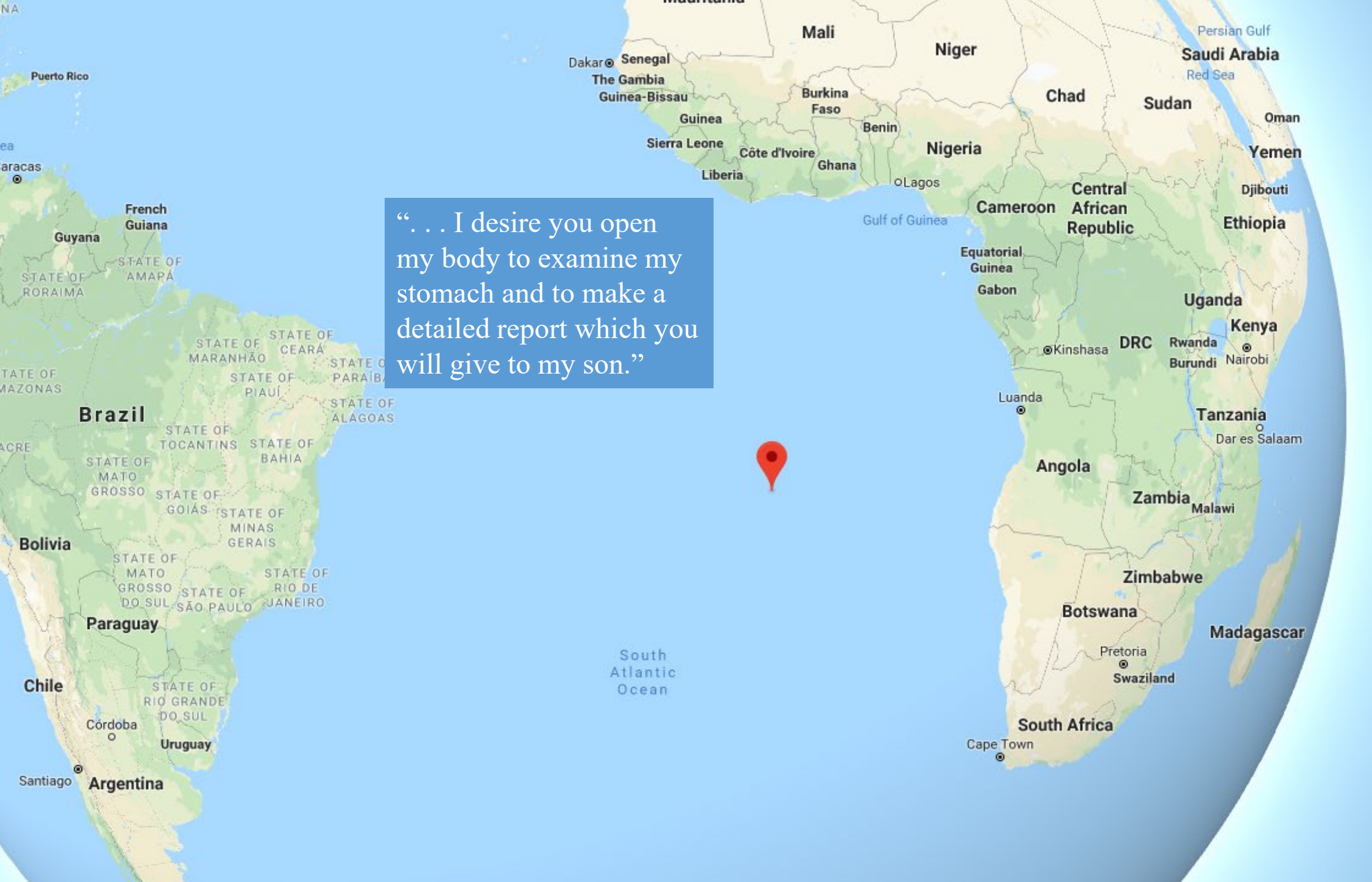
Hereditary Gastric Cancer Syndromes

Syndromes	Genes	Inheritance	Gastric cancer risk, %
Hereditary diffuse gastric cancer syndrome	<i>CDH1</i>	Autosomal dominant	56–70
Gastric adenocarcinoma and proximal polyposis syndrome	Implicated gene unknown	Autosomal dominant	Not determined
Hereditary nonpolyposis colon cancer	<i>MLH1, MSH2</i> <i>MSH6, PMS2</i>	Autosomal dominant	2–30
Peutz-Jeghers syndrome	<i>STK11</i>	Autosomal dominant	29
Juvenile polyposis	<i>SMAD4, BMPR1A</i>	Autosomal dominant	21
Familial breast cancer	<i>BRCA1, BRCA2</i>	Autosomal dominant	5.5 2.6
Li-Fraumeni syndrome	<i>TP53</i>	Autosomal dominant	3.1–4.9
Familial adenomatous polyposis	<i>APC</i>	Autosomal dominant	2.1–4.2

(Asia 4-13%)

Islands and Diffuse Hereditary
Gastric Cancer Syndrome...





"... I desire you open my body to examine my stomach and to make a detailed report which you will give to my son."

Napolean Bonaparte Pedigree

6

S. Bevan and R.S. Houlston

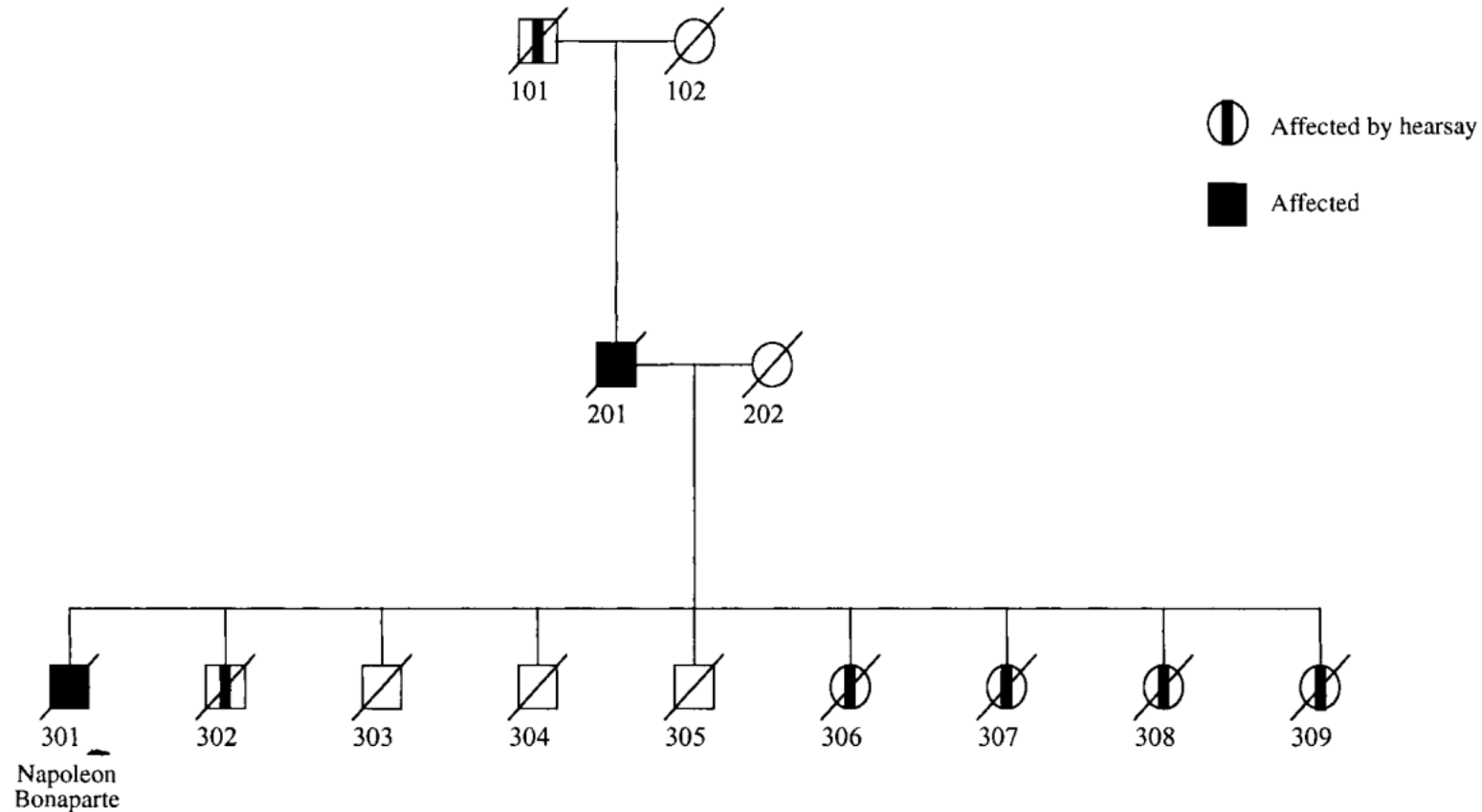


Figure 1. Pedigree of the Bonaparte family. Napoleon, his father, grandfather, brother and four sisters all died of stomach cancer.



letters to nature

E-cadherin germline mutations in familial gastric cancer

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Familial gastric cancer in a kindred of Maori ethnicity was originally reported in 1964 and in the past 30 years over 25 family members have died of this disease.

The age of death from gastric cancer ranges upwards from 14 years of age, with the majority of cases occurring in people under the age of 40.

CDH1 (E-cadherin) pathogenic mutation

- Average age of onset of diffuse gastric cancer is ~38
- Cumulative risk of gastric cancer in CDH1 carriers of pathogenic mutation by age 80:
 - Men = 70%
 - Women = 56%
- Cumulative risk of Lobular breast cancer in CDH1 carriers of pathogenic mutation by age 80:
 - Women = 42%



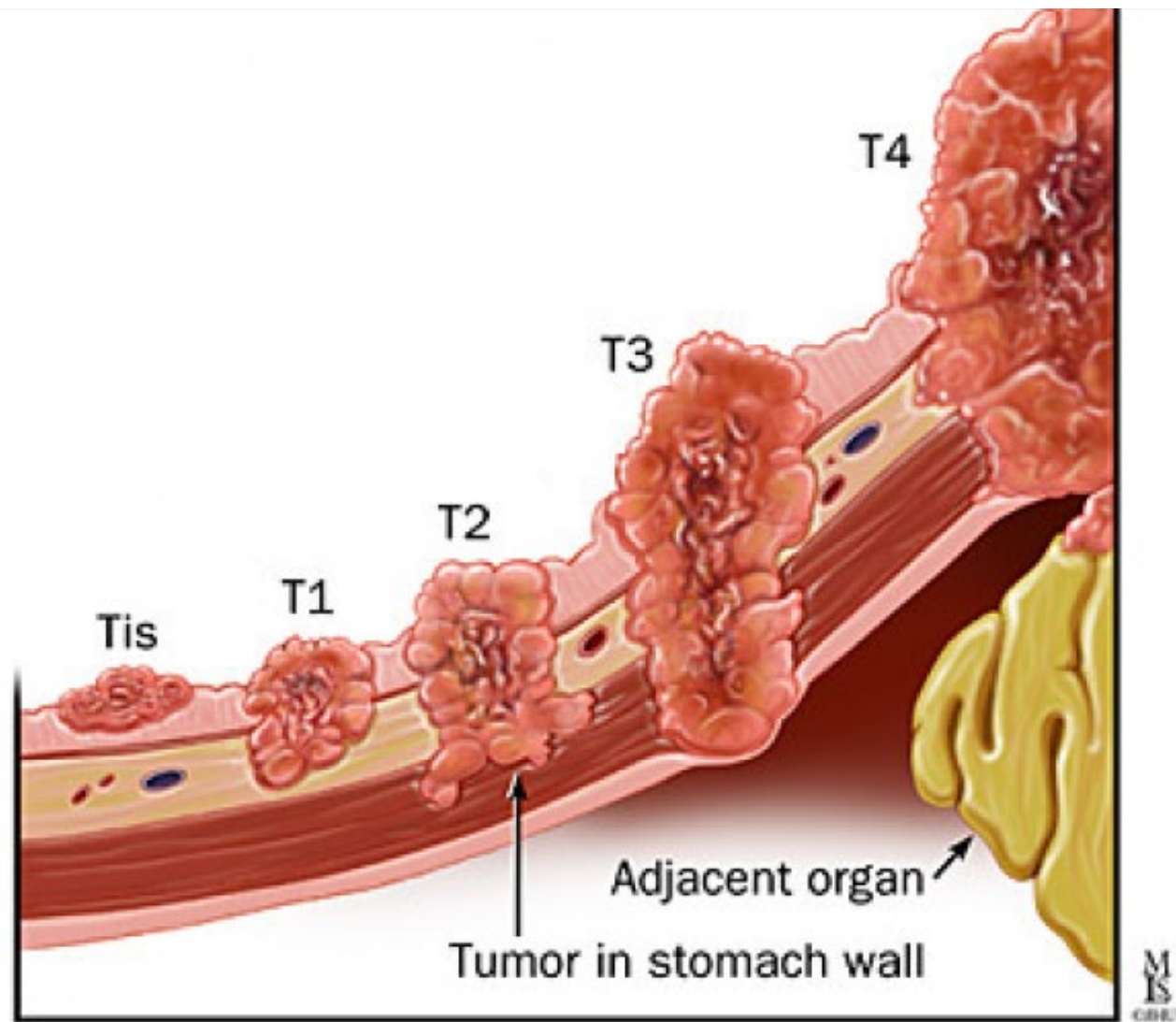
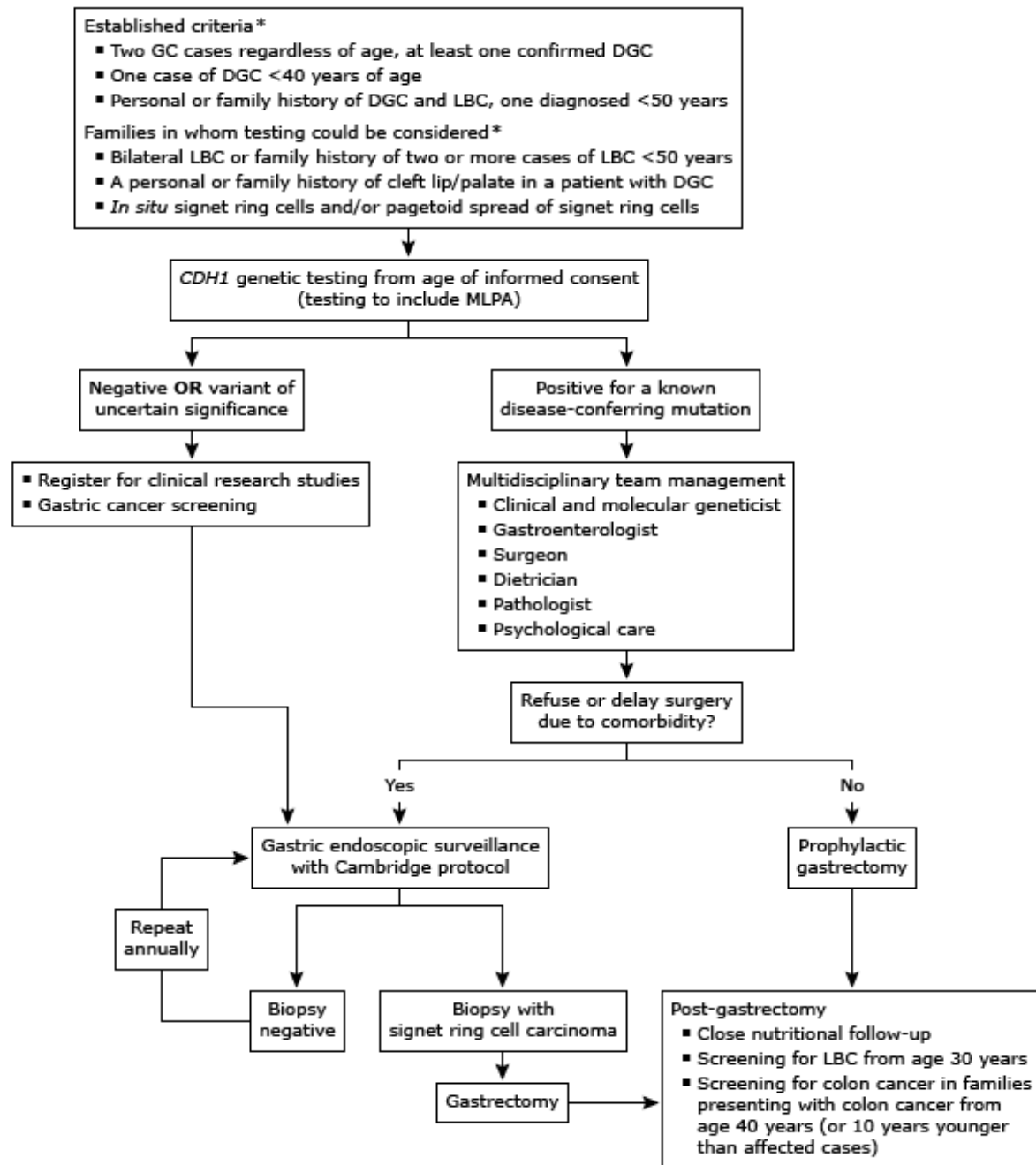


Figure 17. TNM staging of gastric cancer, showing depth of invasion.



International Gastric Cancer Linkage Consortium

Defined Clinical Criteria and pathways of care

Wanaka Testing Criteria

CDH-1 and if negative → CTNNA1

Individual Criteria

- Diffuse Gastric Cancer
 - Individual <50
 - Maori
 - And Lobular Breast CA <70
 - Cleft lip or palate in individual or family
- Invasive Lobular Breast Cancer
 - Individual with Bilateral disease <70
- Gastric in situ or pagetoid spread <50 years old

Family Criteria

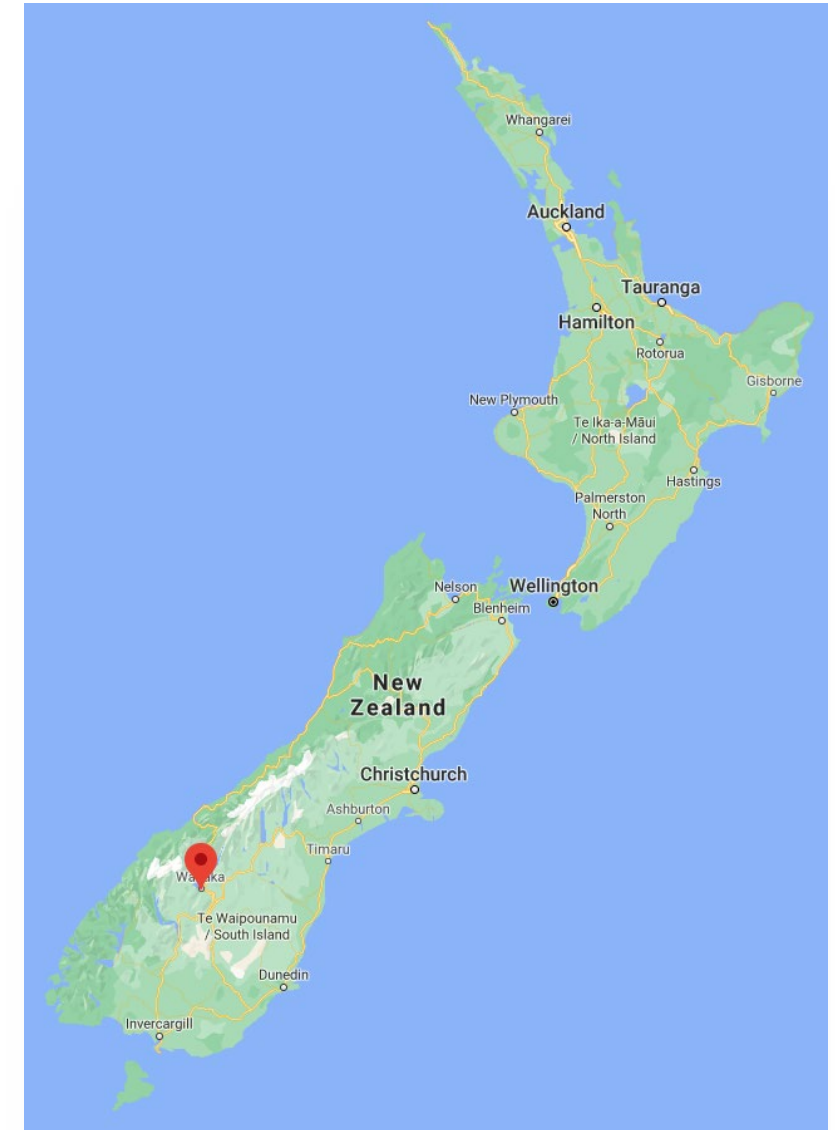
- Diffuse Gastric Cancer
 - ≥ 2 family members with 1 DGC
- Invasive Lobular Breast Cancer
 - > 2 cases in family members <70
- DCG & LBC in different family members
 - DCG any age
 - LBC <70

Wanaka Treatment Guidelines

“*CDH1* variant carriers from families with confirmed HDGC should be advised to consider prophylactic total gastrectomy, irrespective of endoscopic findings”

“Where possible, surgery is recommended in early adulthood, generally between 20 and 30 years of age.”

“prophylactic total gastrectomy is not recommended in patients older than 70 years unless there are noteworthy mitigating circumstances.”



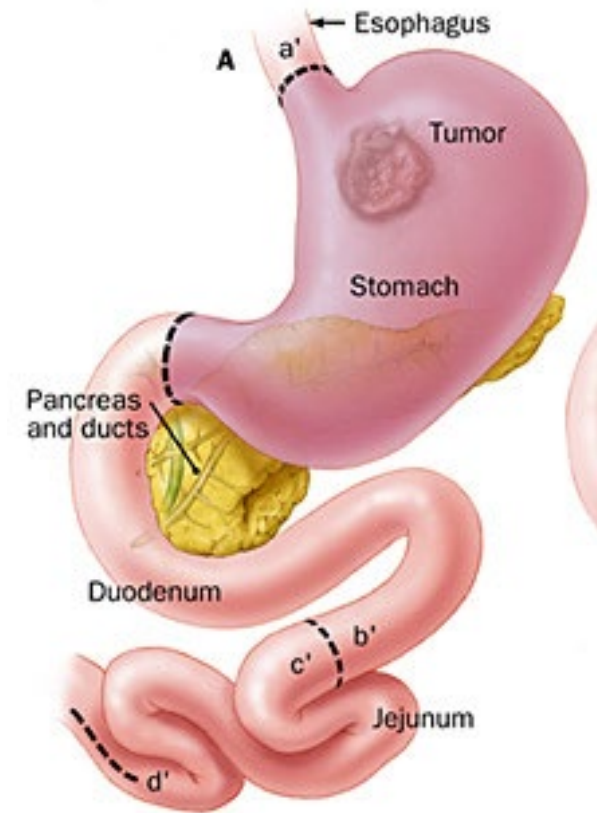


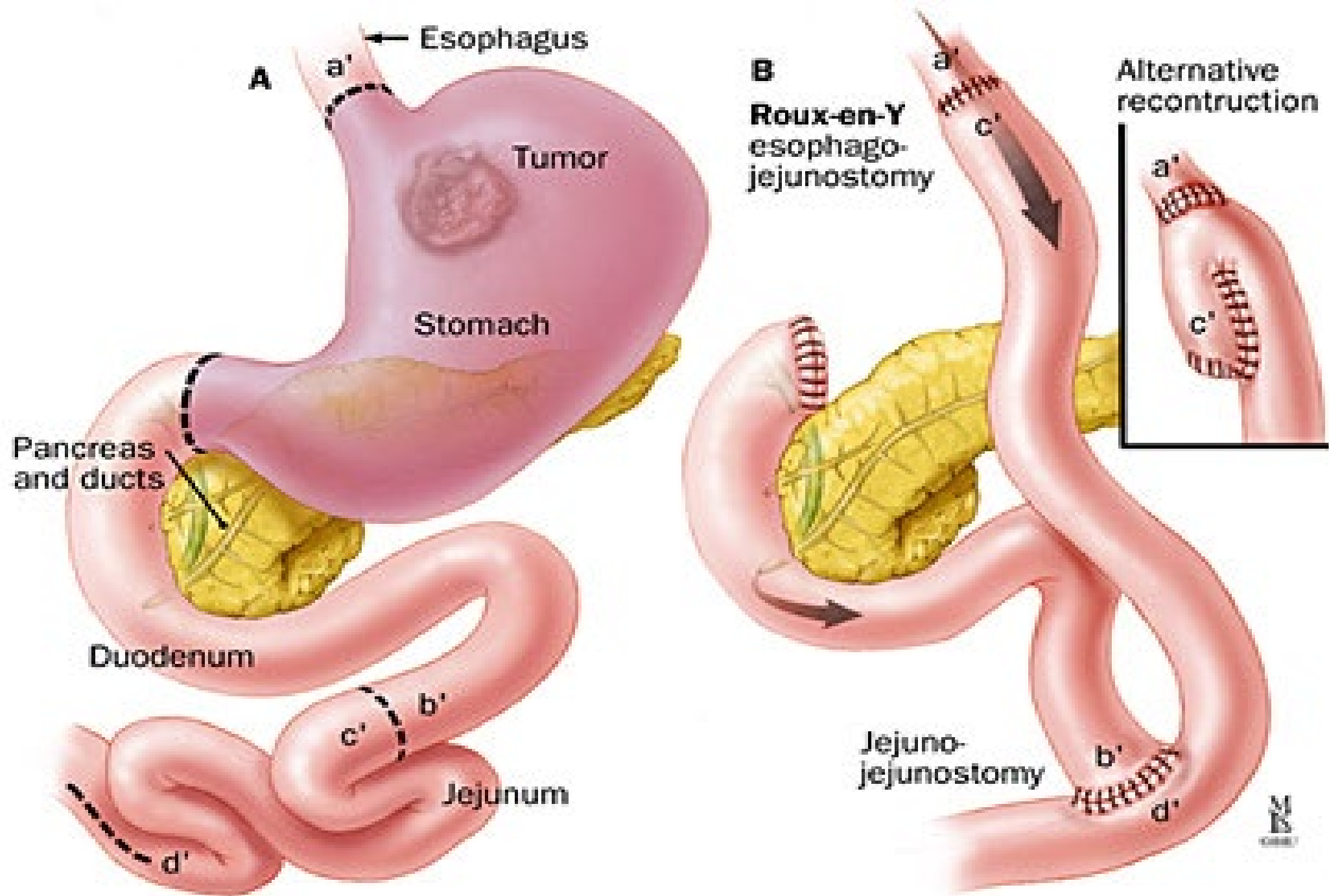
Wanaka Guidelines

- For individuals declining or wishing to postpone gastrectomy, yearly endoscopy by experienced endoscopists with knowledge of HDGC is recommended
- It is also recommended that *Helicobacter pylori* is eradicated if present.
- LBC risk should be managed with either yearly surveillance or bilateral risk-reducing mastectomy.

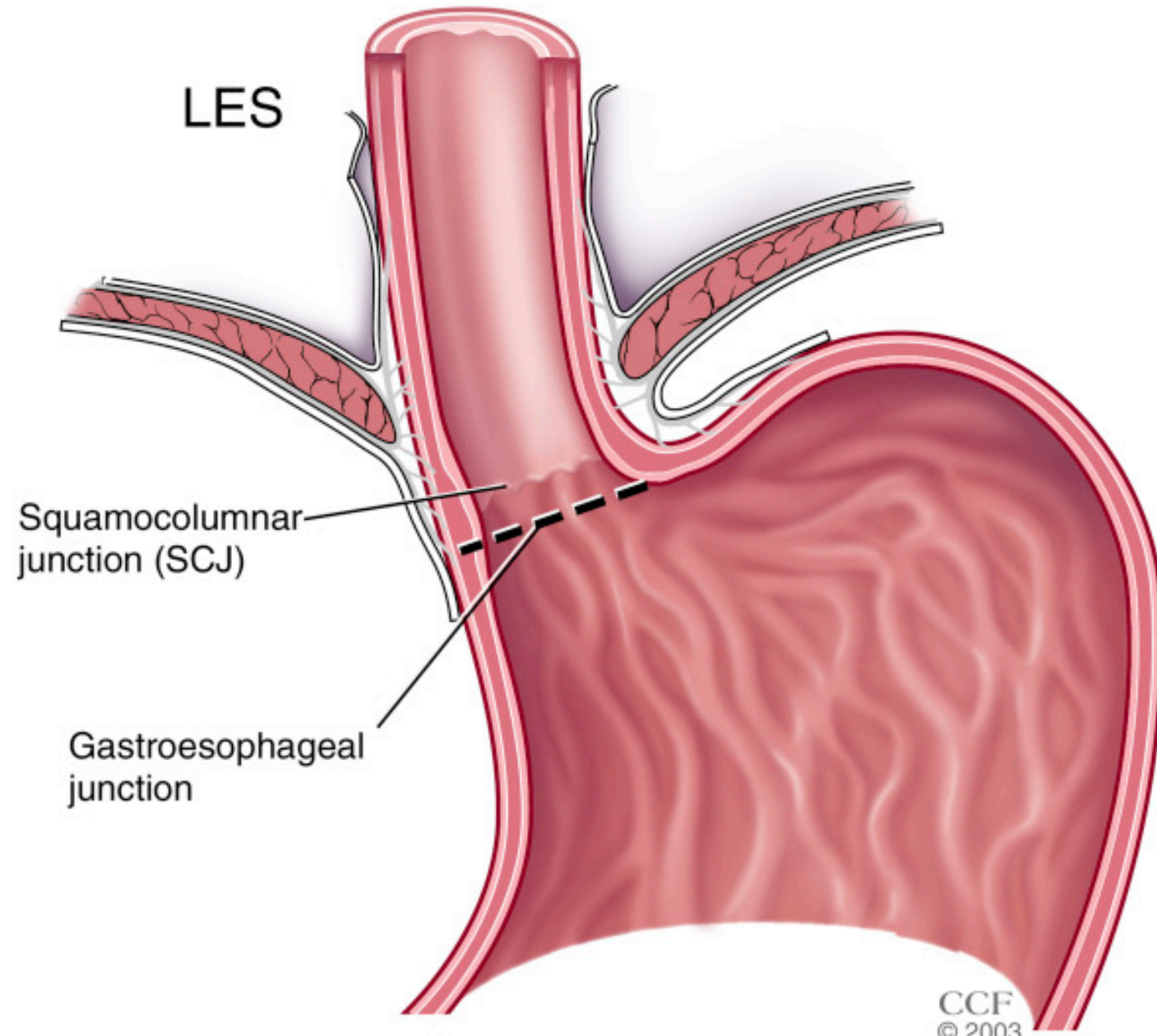
Goal of Total Gastrectomy

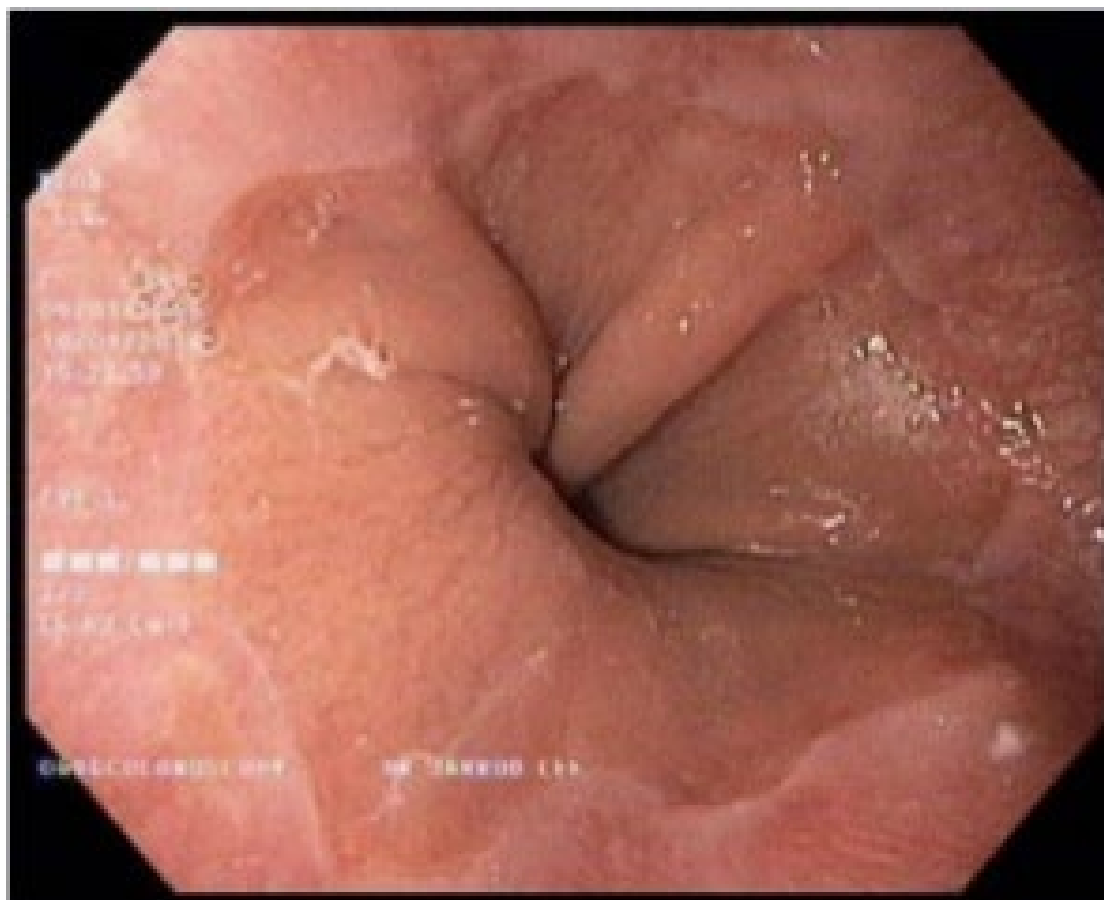
- Removal of all at risk gastric tissues
- Safe reconstruction of esophageal to jejunal (small intestine) connection
 - Avoid bile reflux
 - Ensure good long-term nutrition

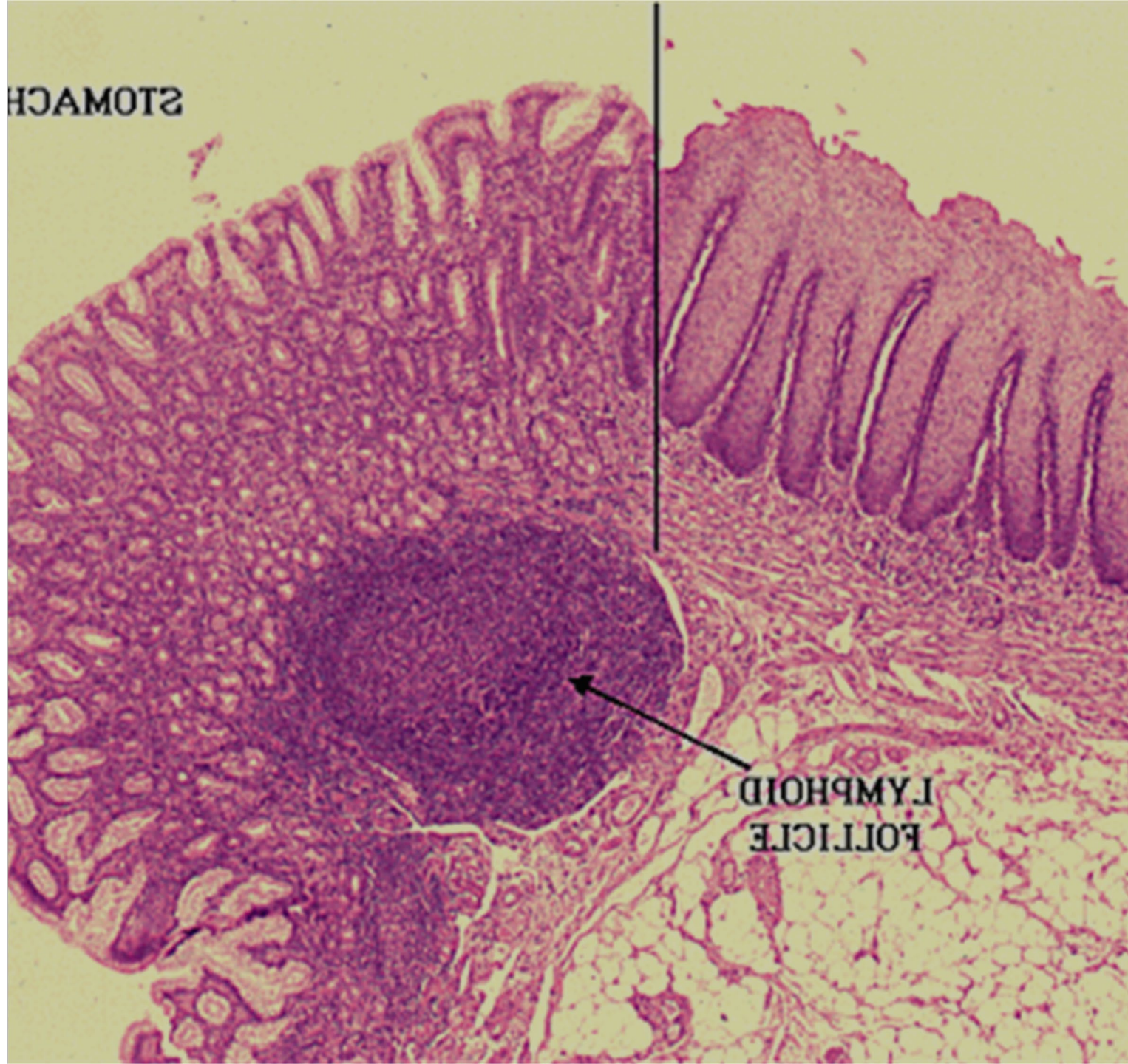




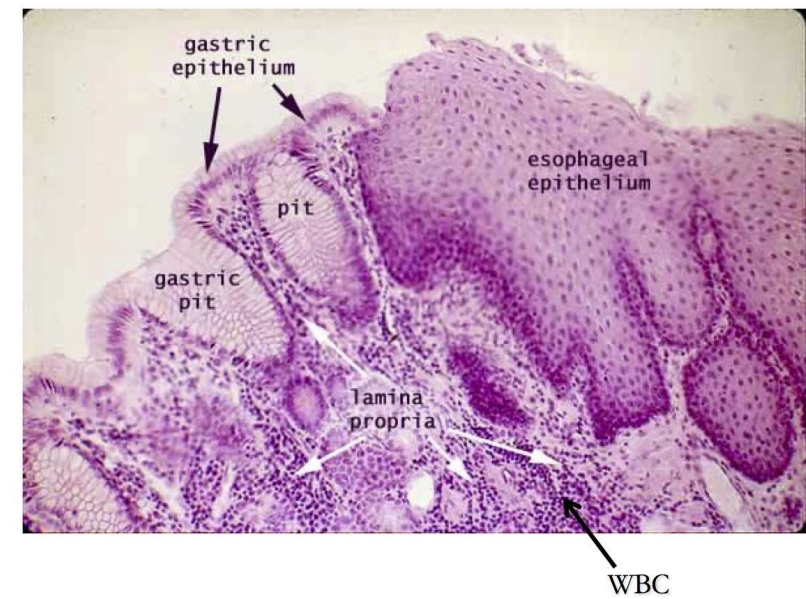
Normal Esophagus

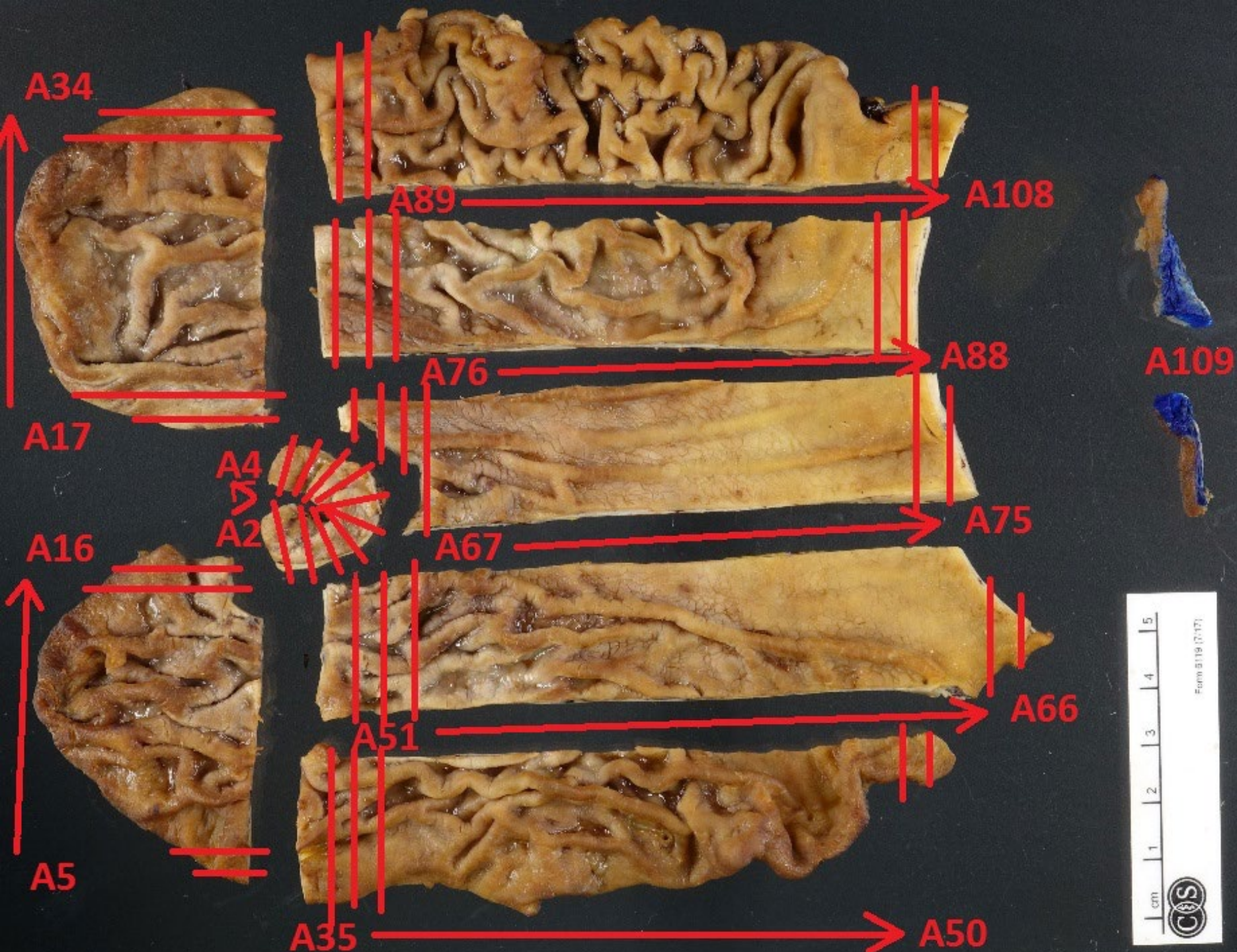






Esophagus - Stomach Junction





“Prophylactic” gastrectomy

TABLE 1 Characteristic of the 13 asymptomatic patients with CDH1 mutation who underwent gastrectomy

Kindred	Age (years)	Mutation	Sex	Positive endoscopy	Outcome	TNM	Follow-up (months)
1	53	1003C>T	F	No	DF	T1N0M0	55
1	52	1003C>T	F	No	DF	T1N0M0	51
1	55	1003C>T	F	No	DF	T1N0M0	51
1	50	1003C>T	F	No	DF	T1N0M0	51
1	56	1003C>T	M	No	DF	T1N0M0	49
1	51	1003C>T	M	No	DF	T1N0M0	49
1	26	1003C>T	M	No	DF	T1N0M0	6
2	70	1565+2insT	F	Yes	DF	T1N0M0	21
2	18	1565+2insT	F	No	DF	T1N0M0	1
3	42	2395delC	F	Yes	DF	T1N0M0	37
4	47	49-2A>C	M	No	DF	T1N0M0	6
5	50	1792C>T	F	No	DF	T1N0M0	7
6	47	233C>T	F	No	DF	No tumor	4

DF disease free

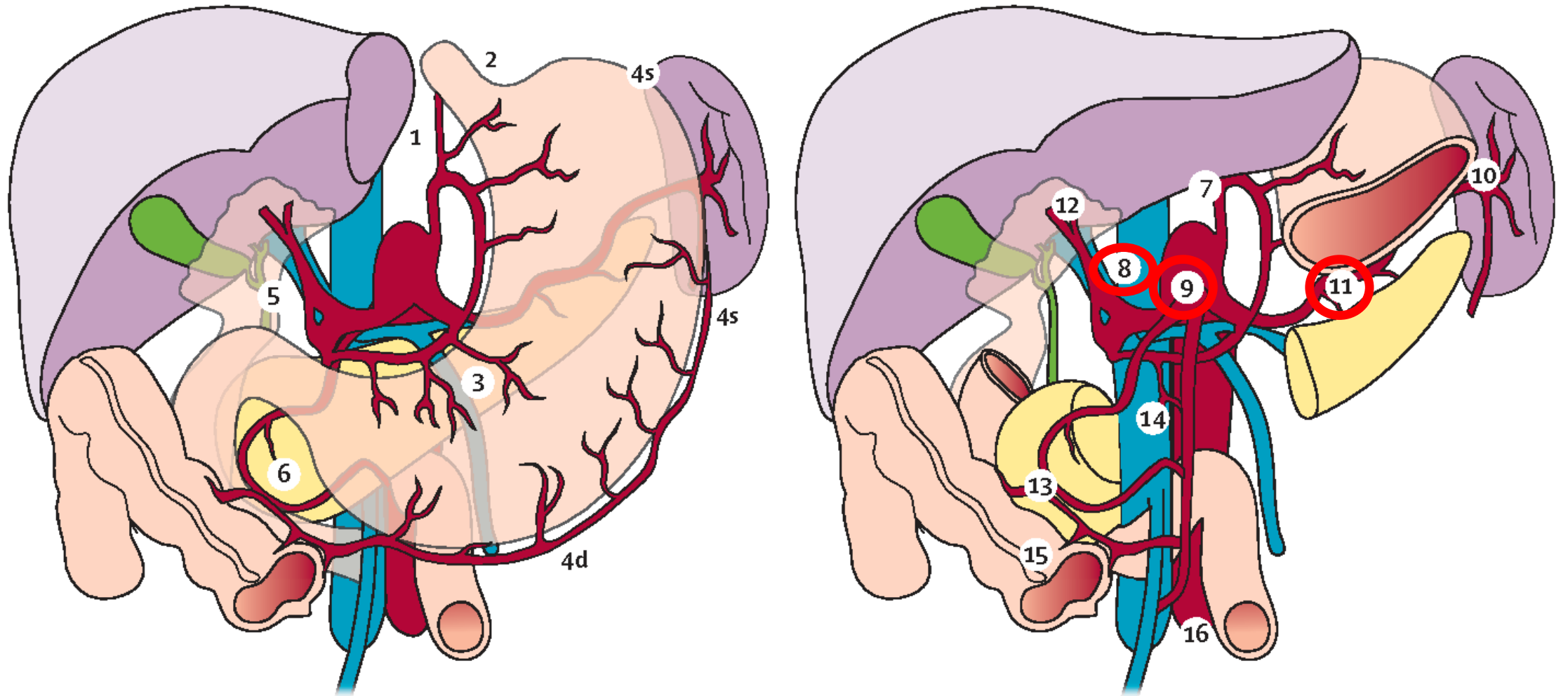
Symptomatic patients

TABLE 2 Characteristic of the five symptomatic patients with CDH1 mutation who underwent gastrectomy

Kindred	Age (years)	Mutation	Sex	Symptoms	Endoscopy	TNM	Clinical course	Follow-up (months)
2	47	1565+2insT	F	GERD	Grossly positive	T4 N2 M0	DOD	17
2	39	1565+2insT	F	ABD pain	Grossly positive	T3N1 M0	Pelvic mets	45
7	52	IVS6 833-2A>G	M	Early satiety and weight loss	Grossly positive	T3N1M0	DOD	23
8	23	49G>T	F	ABD mass	Grossly positive	T3N0M1	DOD	8
9	38	2064delTG	M	Nausea, vomiting, ABD pain	Grossly positive	T1N0M0	DF	48

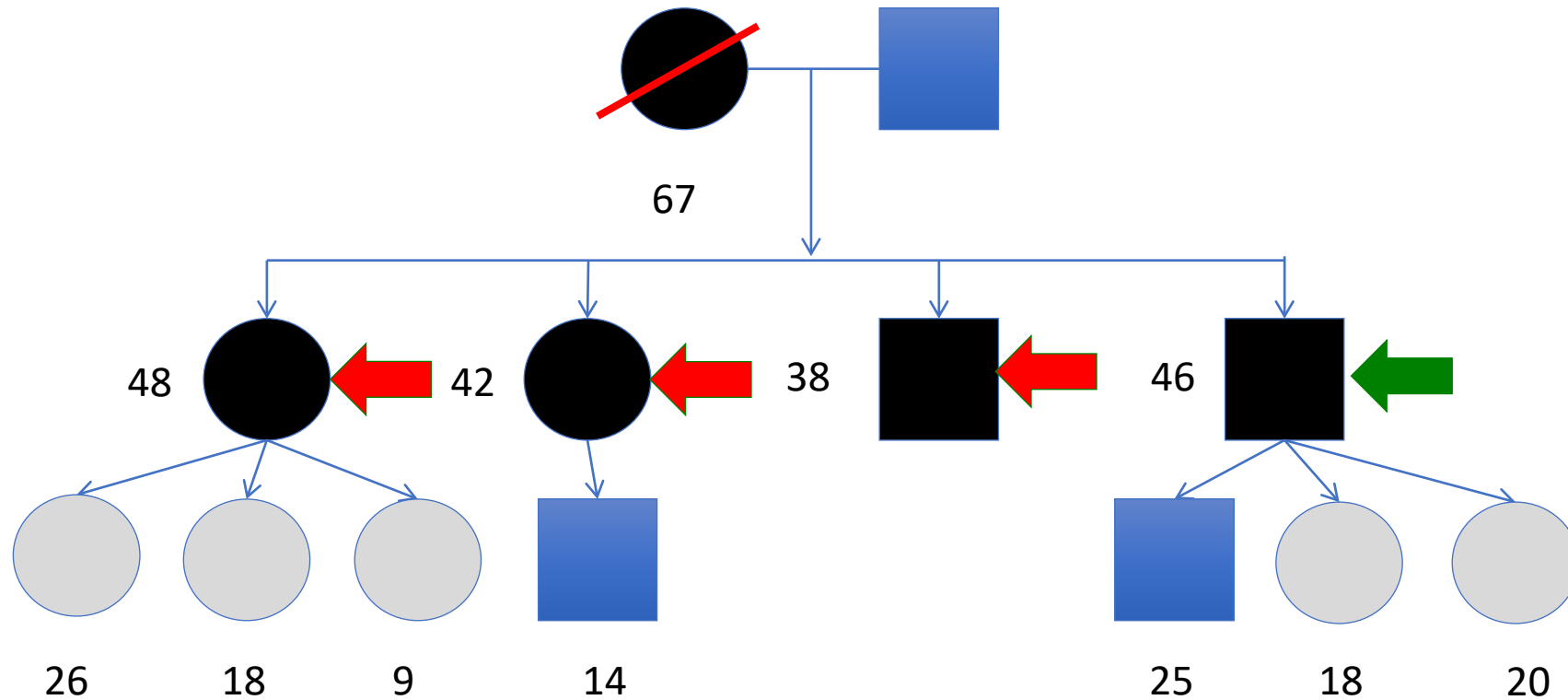
DOD died of disease, *DF* disease free, *ABD* abdominal

D1+ vs D2



Special Circumstances

No gastric cancer CDH1 Cohort



Negative EGD with random biopsies

DIAGNOSIS:

A. STOMACH, PROPHYLACTIC TOTAL GASTRECTOMY:

- Multifocal (at least 20) signet ring cell carcinoma (invasive adenocarcinoma, diffuse type and in-situ adenocarcinoma), see synoptic report below
 - All foci limited to the superficial lamina propria
 - Foci of adenocarcinoma concentrated in the fundus and proximal body
 - Largest focus 2.5 mm, located in mid body along lesser curvature
- Esophagus and duodenum, negative for carcinoma

DIAGNOSIS:

A. STATION 1, BIOPSY:

- Fibroadipose tissue, negative for carcinoma
- No lymph nodes identified

B. STOMACH, PROPHYLACTIC TOAL GASTRECTOMY:

- Numerous foci (at least 40) of invasive and in situ adenocarcinoma with signet-ring cell features, diffuse type
 - All foci are limited to the superficial lamina propria
 - Foci of adenocarcinoma concentrated in the proximal body
- Esophagus and duodenum, negative for carcinoma
- Please see synoptic report below for staging details

Large European Study

- 26 CDH1 or CTNNA1 patients
- "Esophagus was resected 2-3cm (1 inch) above the externally visible gastro-esophageal junction"
 - 36% of patients required greater resection because of positive margins on pathologic examination (frozen sections)
- 88% had Signet Ring Cell foci
- Weight loss stabilized ~12-24 months

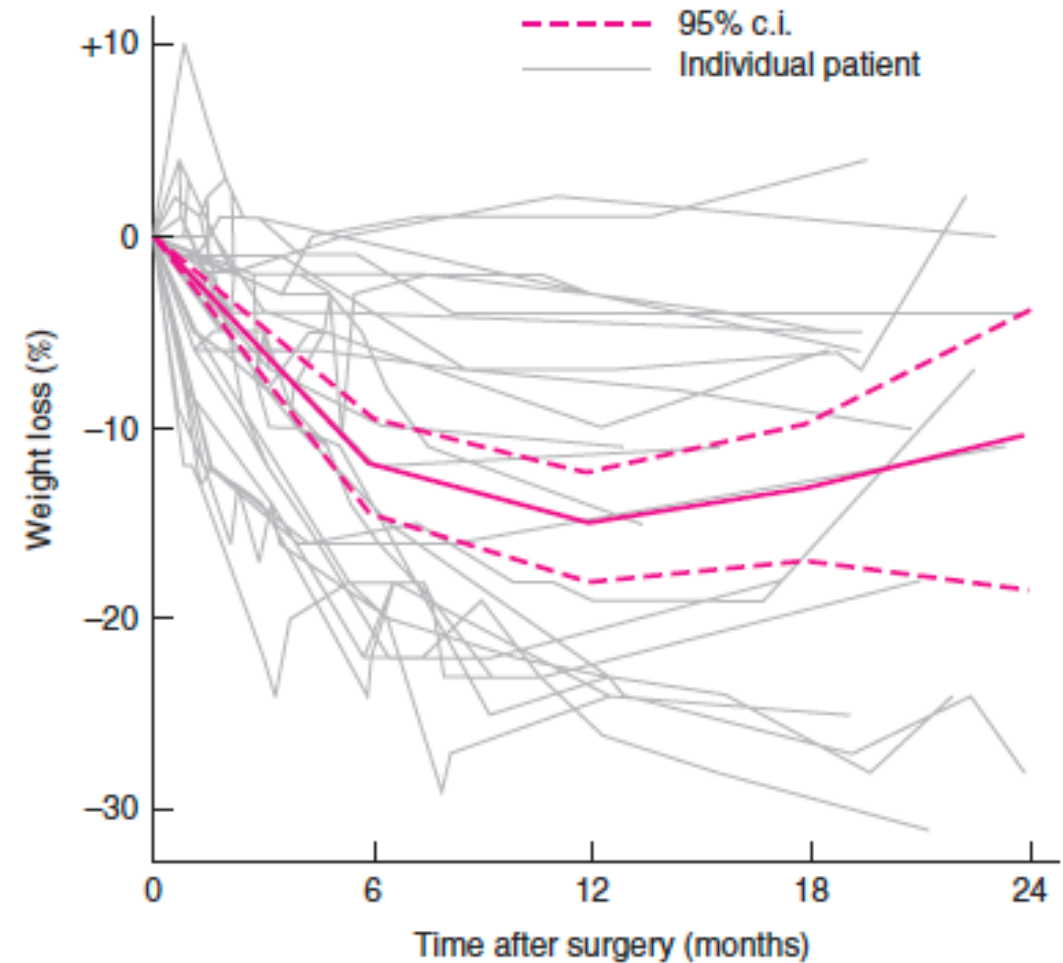
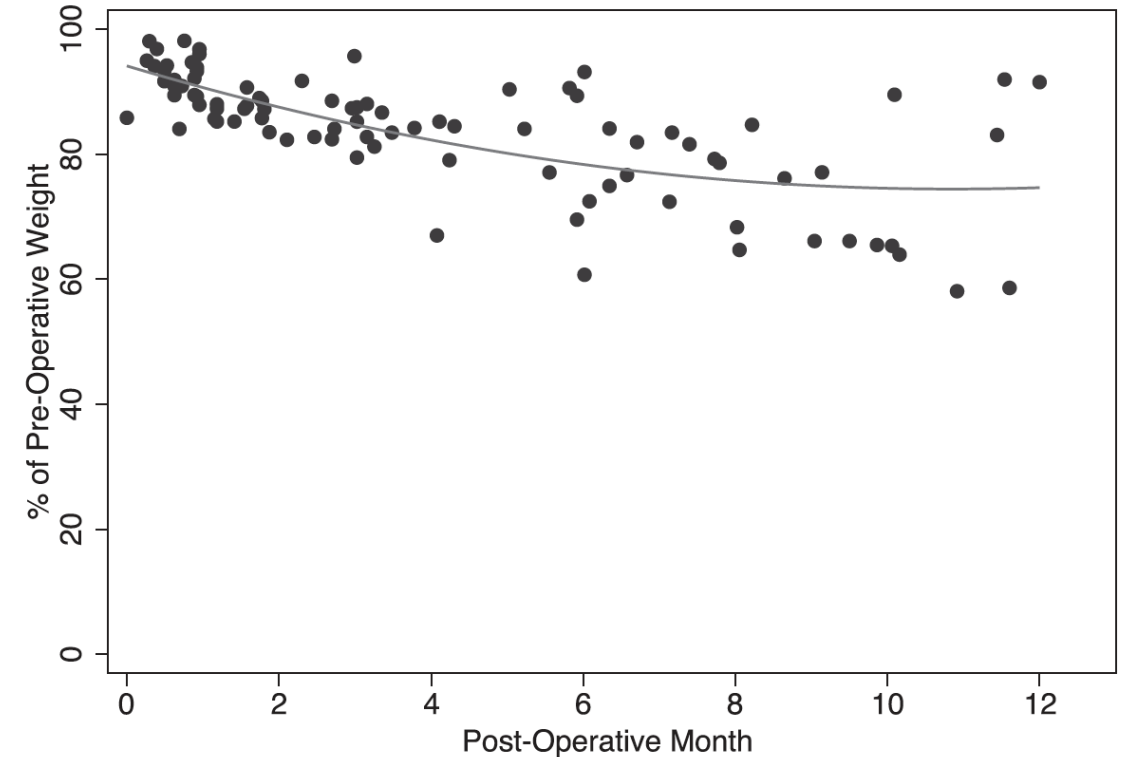


Fig. 1 Weight loss following prophylactic gastrectomy

Large American Study

- 41 CDH1 or CTNNA1 patients
- 25 open – 16 minimally invasive
- 27% complications (1 mortality)
- 85% foci of signet ring cell
- Weight loss stabilized ~12 months
- 40% "as expected" – 45% "better than expected"
- Frozen sections guided completion



MSKCC-10 Questions

	Total Gastrectomy for Cancer (n = 35)	Total Gastrectomy for CDH1 Patients (n = 20)
1. Can you eat as much in a single meal as compared to before your surgery? (YES)	5 (14%)	7 (35%)
2. Are there any foods you can no longer tolerate? (YES)	17 (49%)	8 (40%)
3. Approximately how many times per day do you eat? (Median and range in times/day)	5 (3–8)	5 (3–8)
4. What is your weight now relative to pre-op weight?		
I. Higher	2 (6%)	2 (10%)
II. Same	4 (11%)	6 (30%)
III. Lower	29 (83%)	12 (60%)
5. After eating, do you experience any of the following symptoms?		
I. Sweating and/or weakness	10 (29%)	6 (30%)
II. Abdominal discomfort and/or cramping	18 (51%)	9 (45%)
III. Flushing	8 (23%)	2 (10%)
IV. Diarrhea	18 (51%)	3 (10%)
Patients reporting 1 or more symptoms:	27 (77%)	14 (70%)
6. Have you ever had a dilatation? (YES)	3 (9%)	2 (10%)
7. Have you developed any other types of cancer or significant medical problems? (YES)	10 (29%)	4 (20%)
8. Were you employed/working before you had your surgery? (YES)	18 (51%)	18 (90%)
If yes: Did you return to work after your surgery (YES)	13 (72%)	18 (100%)
If yes: Are you currently working? (YES)	7 (54%)	18 (100%)
9. How does your overall QOL now measure up to your expectations before surgery?		
Better	22 (63%)	9 (45%)

Strong. Ann Surg, 2017.

Large American Study

In Summary

- CDH1 pathogenic mutations we recommend risk reducing prophylactic gastrectomy
- Surveillance is important but can frequently miss submucosal lesions
- When considering gastrectomy – seek out high volume centers experienced in gastric cancer management

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