Genetics and Management of Hereditary Diffuse Gastric Cancer

South Florida GI Cancer Symposium
April 11, 2025

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Outline

- Case 1
- Germline CDH1 mutation and risk of cancer
- Endoscopic surveillance
- Microscopic foci of SRCC
- Prophylactic total gastrectomy

Case 1

The NEW ENGLAND JOURNAL of MEDICINE

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 22-2007: A Woman with a Family History of Gastric and Breast Cancer

Daniel C. Chung, M.D., Sam S. Yoon, M.D., Gregory Y. Lauwers, M.D., and Devanshi Patel, M.S., C.G.C.

Chung DC, Yoon SS et al. N Engl J Med 2007;357:283-91

Patient 1 -- AM

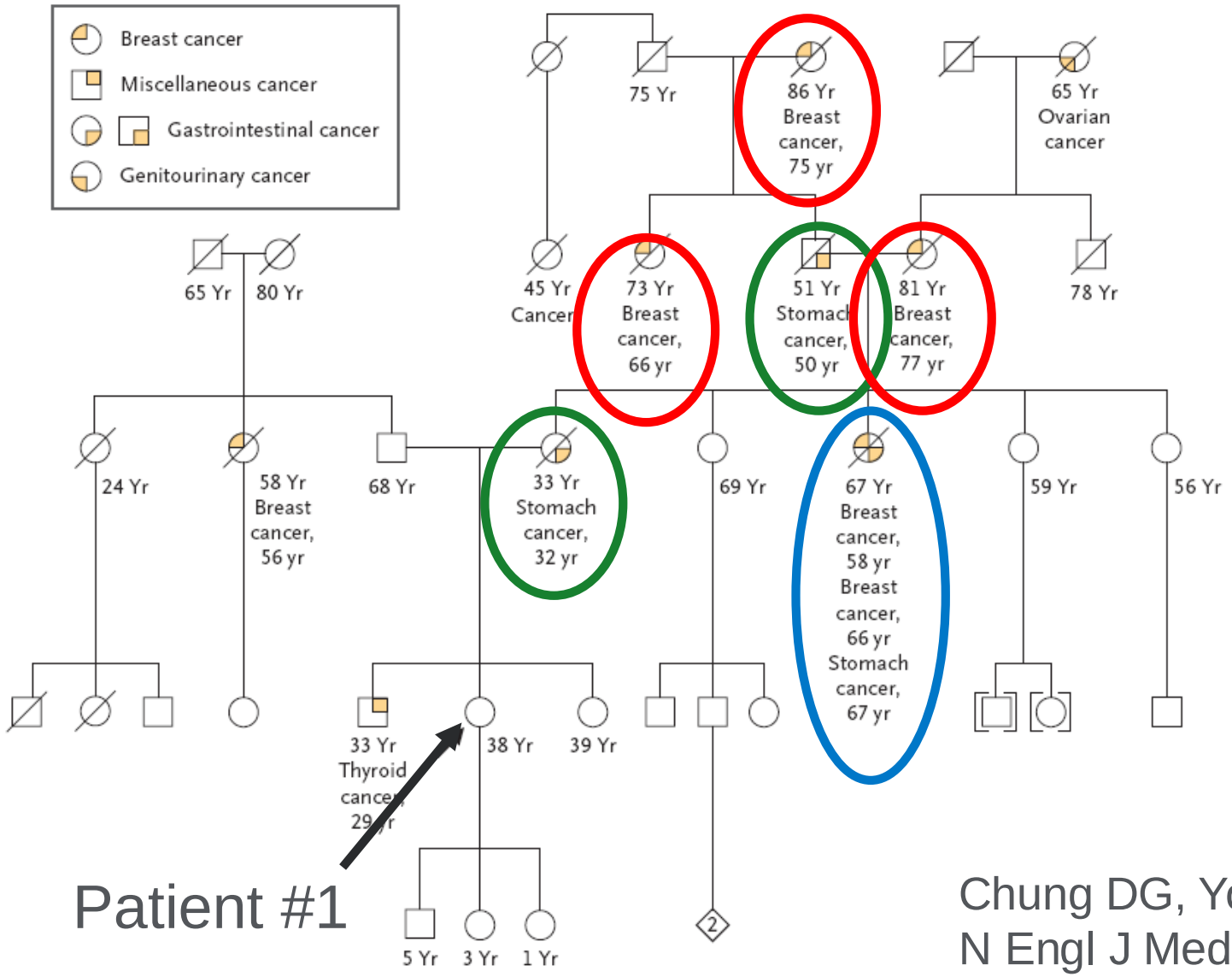
- 38 yo woman with strong FH of breast and gastric cancer
  - Mother died at age 33 of gastric cancer
  - Maternal aunt with lobular breast cancer at age 58 and 67, died at 68 of gastric cancer
- Maternal aunt tested for CDH1 mutation leading to R732Q
- Patient underwent genetic counseling and also tested positive for same mutation
- EGD with random biopsies negative
- Prophylactic total gastrectomy in April 2006

Dogma in 2006

- Risk of DGC in those with pathogenic germline CDH1 mutations is high
  - Lifetime risk 83% is women and 67% in men
- Endoscopic surveillance is not adequate
  - >90% of patients undergoing PTG after negative endoscopy have microscopic foci of early SRCC
- Microscopic foci of early SRCC will ultimately progress to a clinically significant cancer
- Risk of HDGC markedly outweigh risk of PTG and impact on QOL

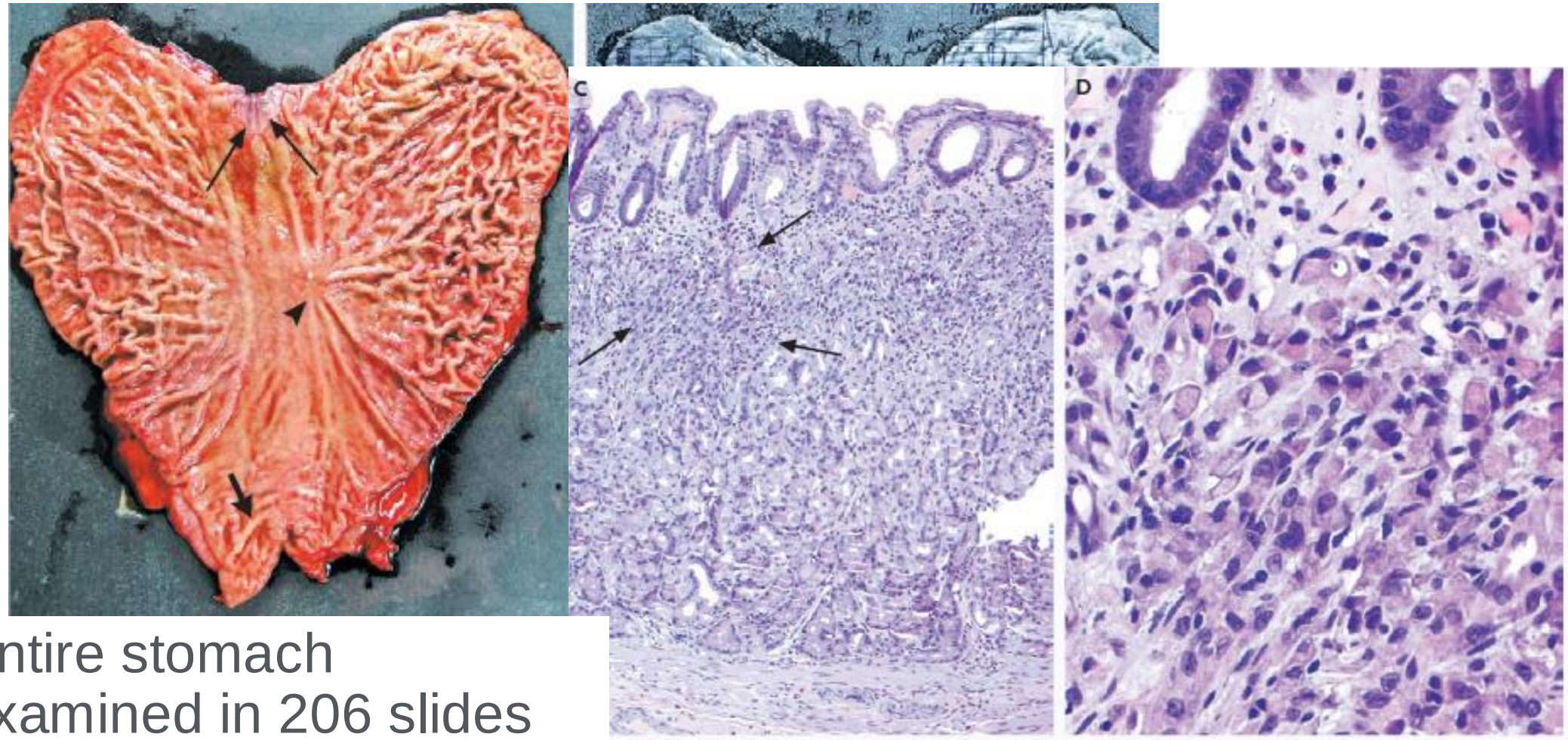
Pharoah PD et al. Gastroenterol 2001:121:1348
Hebbard PC Ann Surg Oncol 2009:16:1890

Patient #1 Family Pedigree



Chung DG, Yoon SS, et al.
N Engl J Med 2007;357:283-91

Prophylactic Gastrectomy Pathology



- Entire stomach examined in 206 slides
- One 2mm focus intramucosal DGC found

Fujita H, Yoon SS et al Am J Surg Pathol 2012:36:1709-17

Germline CDH1 Mutation and Risk of Cancer

Hereditary Gastric Cancer

- About 10% of gastric cancers exhibit familial clustering and
  - 1-3% linked to a hereditary syndrome
- Ambry's BRCAPlus panel, CustomNext panel, and +RNAinsight test which in total includes analysis of 40 genes including all genes in table

Genetic loci	Syndrome	Gastric cancer risk	Other cancer risks
CDH1	Hereditary diffuse gastric cancer (HDGC)	Up to 70%	Lobular breast
CTNNA1	HDGC	Up to 57%	Lobular breast
STK11	Peutz-Jeghers syndrome	29%	Breast, GI, pancreas, ovarian, lung, GYN
SMAD4, BMPR1A	Juvenile polyposis	21%	Colon, pancreas, small bowel
MLH1, MSH2, MSH6, PMS2	Lynch syndrome	1% - 13%	Colon, ovarian, uterine, urinary tract, other
APC	Familial adenomatous polyposis	1% - 2%	Colon, duodenum, thyroid
APC promoter 1B	Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	12 - 25%	Unknown, possibly colon
MUTYH	MUTYH-associated polyposis	2%	Colon, duodenal, ovarian, bladder, skin

Lerner BA et al. Curr Treat Options Gastroenterol 2020:18:604

CDH1, E-cadherin, and Cancer

- *CDH1* encodes for E-cadherin
  - Transmembrane glycoprotein expressed on epithelial tissues
  - Responsible for cell-to-cell adhesion
- Loss of E-cadherin promotes tumorigenesis
- Somatic mutations or promoter methylation occur in 40-80% of sporadic diffuse gastric cancers and majority of sporadic lobular breast cancers

Grunwalt GB Curr Opin Cell Biol 1993:5:797-805
Grady WM et al. Nat Genet 2000:26:16-17

Discovery of *CDH1* Germline Mutation

- Early onset familial gastric cancer described in 3 Maori families in 1964
  - 25 family members died of gastric cancer over next 30 years
  - Youngest family member was 14 years old
- Parry Guilford and colleagues performed genetic linkage analysis with microsatellite markers in a large Maori kindred
  - Found significant linkage to markers flanking *CDH1* gene
  - Identified germline mutation in *CDH1* in 1999
- Few hundred kindred with germline *CDH1* pathogenic variants identified worldwide

Jones N Z Med J 1964:63:287-296
Guilford et al Nature 1998:392:402-405
Kaurah et al. JAMA 2007: 297:2360-72

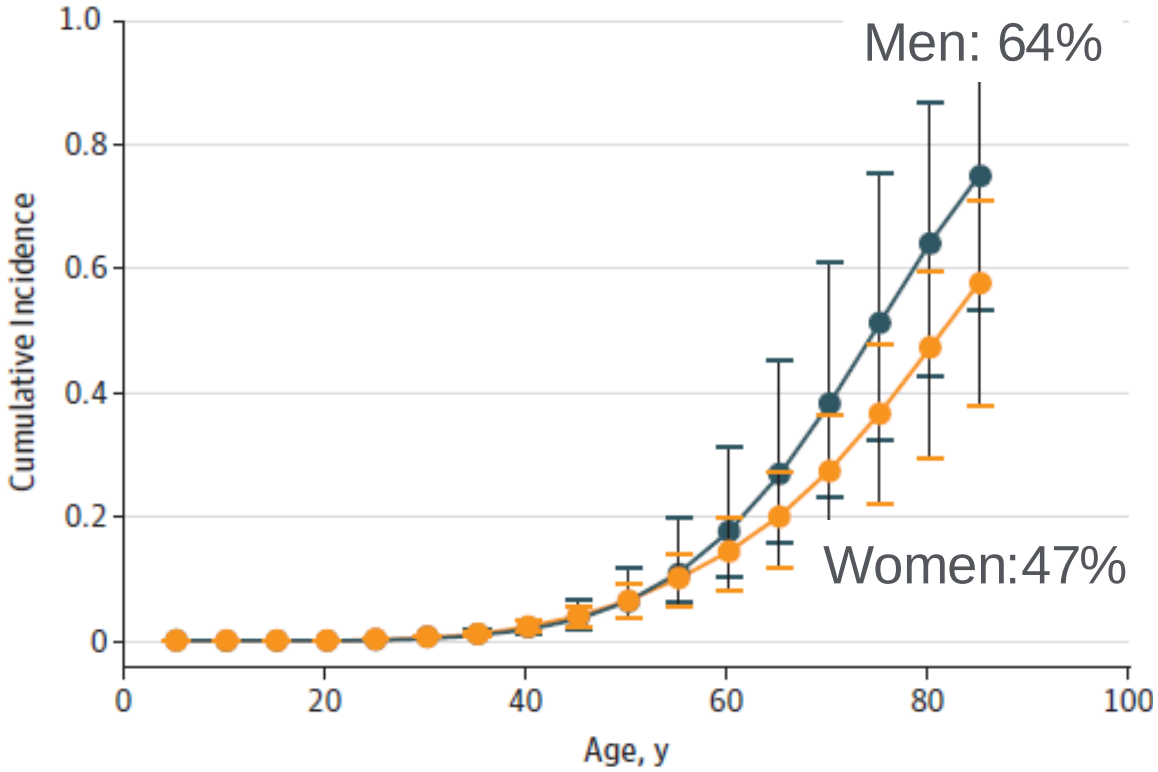
CDH1 Germline Mutation and Risk of Hereditary Diffuse Gastric Cancer: 2025

- Penetrance analysis of 38 families with pathogenic *CDH1* mutations identified by multigene testing panel at large American commercial lab
  - Men: 37% risk
  - Women 24% risk
  - Early vs advanced disease?
- Penetrance analysis of 41 families with pathogenic *CDH1* mutations identified by multigene testing panel at different commercial lab
  - Men: 42% risk
  - Women 33% risk
  - Early vs advanced disease?
- Multicenter study of 213 families, 7323 individuals with P or LP CDH1 mutation
  - pT1aN0/stage IA separate and distinct from stage II-IV (advanced gastric cancer)
  - Prevalence of gastric cancer 13.9%, breast cancer 26.3%
  - Cumulative risk of advanced gastric cancer by age 80: 10.3% in men and 6.5% in women
  - Cumulative risk of invasive breast cancer by age 80: 36.8%

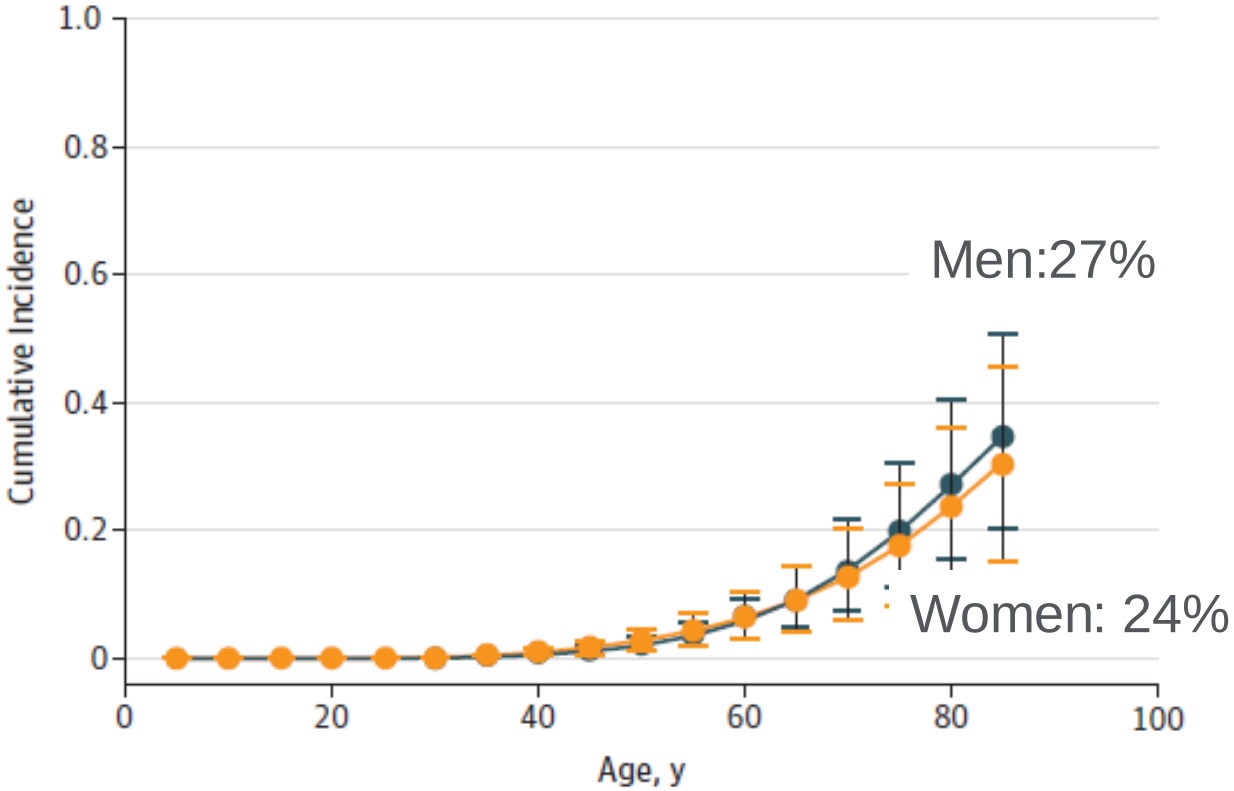
Xicola RM et al. J Med Genet 2019:56:838
Roberts ME et al. JAMA Oncol 2019:5:1325
Ryan CE et al. JAMA 2024:332:722

CDH1 Germline Mutation and Risk of Hereditary Diffuse Gastric Cancer: 2019

Families with 3 or more GC cases



Families with 2 or less GC cases



Roberts ME et al. JAMA Oncol 2019:5:1325

International Gastric Cancer Linkage Consortium: 2020

***CDH1* and *CTNNA1* testing is recommended in the following situations**

Individual criteria

DGC in individuals aged <50 y[a]

DGC at any age in individuals with a personal or family history of cleft lip/cleft palate

History of DGC and LBC in individuals aged <70 y

Bilateral LBC/LCIS in individuals aged <70 y

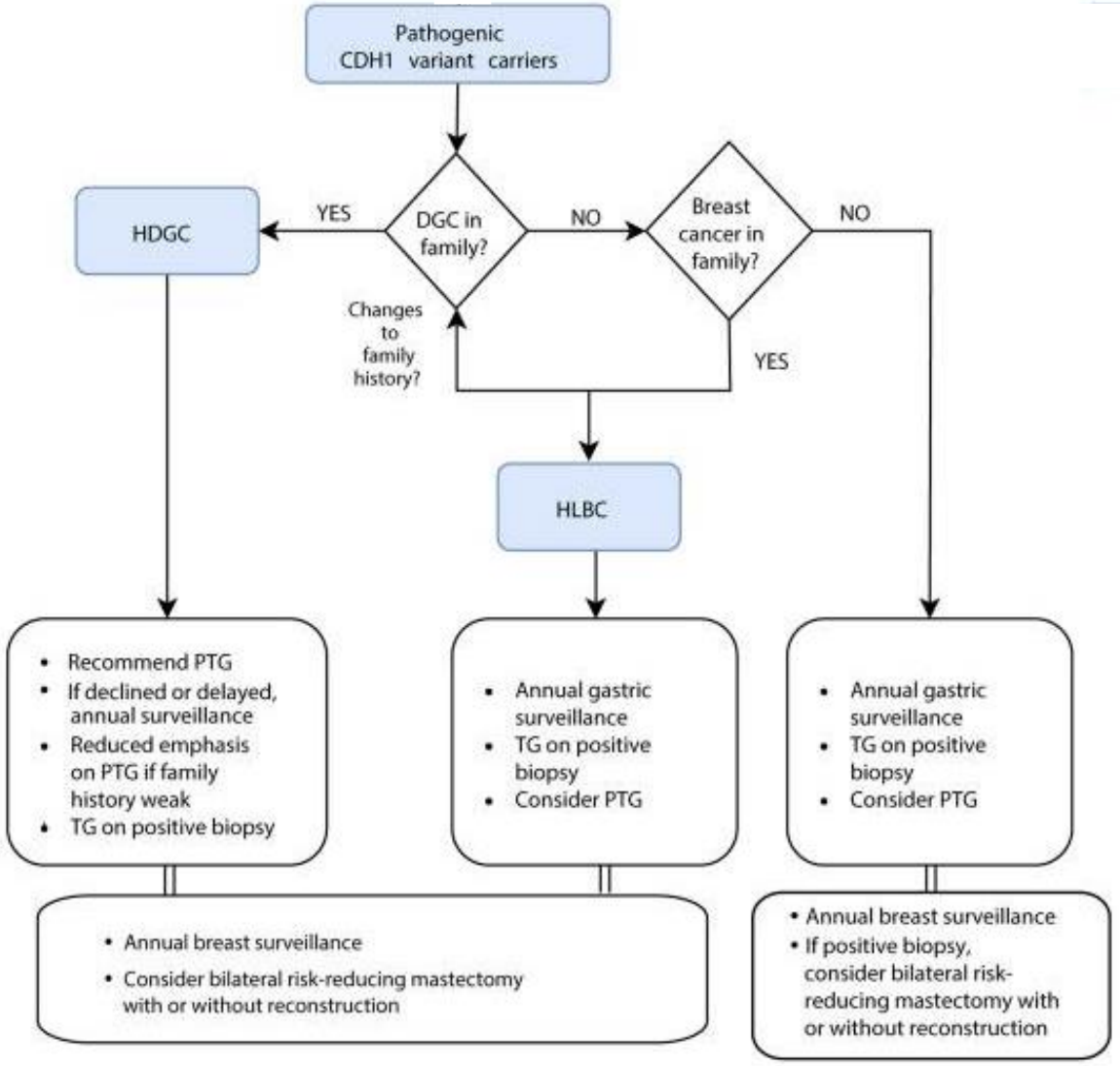
Gastric biopsy with in situ signet ring cells and/or pagetoid spread of signet ring cells in individuals aged <50 y

Family criteria[b]

≥2 Cases of gastric cancer in family (any age), with at least 1 confirmed DGC

≥2 Cases of LBC in family members aged <50 y

≥1 Case of DGC any age and ≥1 case of LBC in different family members aged <70 y



Blair VR et al. Lancet Oncol 2020:21:e386

Endoscopic Surveillance

Endoscopic Screening

- Cambridge method currently standard of care
  - White light examination
  - 5 random biopsies from 6 separate areas
  - Positive 20%-63%
- Screening endoscopies in Japan and Korea routinely detect diffuse gastric cancer at an early and curable stage
- Korean study of 121,111 pts undergoing screening endoscopy, 282 pts had early gastric cancer (pT1a/b)
  - 62% intestinal and 38% diffuse
  - 5 year DFS 97% and 100%

Kumar S et al. World J Gastroenterol 2019:25:2878
Lee JY et al. Gut and Liver 2017:11:807

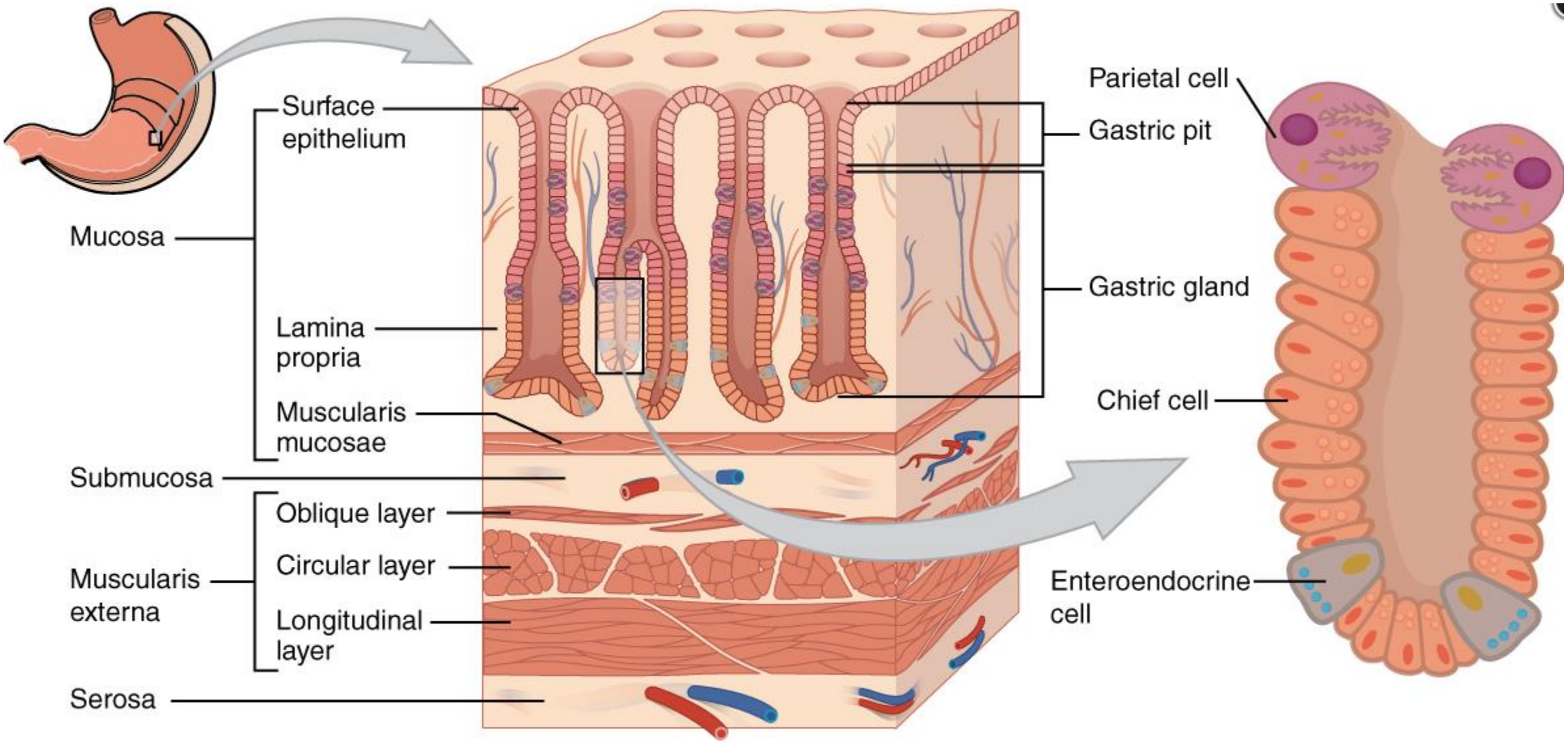
Surveillance Endoscopy in the Management of Hereditary Diffuse Gastric Cancer Syndrome

Madeline Friedman,[*,a] Tomer Adar,[*,a] Devanshi Patel,[‡] Gregory Y. Lauwers,[§] Sam S. Yoon,[‖] John T. Mullen,[¶] and Daniel C. Chung[*,‡]

Clinical Gastroenterology and Hepatology 2021;19:189–191

- 48 CDH1 pts
  - 124 EGDs over 80 person-years
  - 26 with 1 EGD
  - 22 with ≥2 EGDs: mean of 4.4 EGDs over 3.6 years
- 12/22 with ≥2 EGDs underwent PTG
  - 11 with stage 0 or Ia
  - 1 with stage II (T3N0M0) – gastrectomy after 9.4 years of surveillance, receive chemotherapy, NED
- 5 largest studies with 20-102 CDH1 pts undergoing endoscopic surveillance
  - No cases of gastric cancer mortality cited
  - Studies limited by selection bias and short follow-up

Microscopic Foci of SRCC


Surface epithelium
Mucosa
Lamina propria
Muscularis mucosae
Submucosa
Oblique layer
Circular layer
Muscularis externa
Longitudinal layer
Serosa
Parietal cell
Gastric pit
Gastric gland
Chief cell
Enteroendocrine cell

Microscopic Foci of Signet Ring Cell Carcinoma

- For most cancers, penetration of tumors cells through the basement membrane marks a transition to invasive and potentially metastatic disease
- For individuals with pathogenic germline CDH1 mutations, microscopic foci of SRCC into lamina propria or muscularis mucosae (pT1a) are almost universal
- Prevalence of pT1a SRCC in prophylactic gastrectomy specimens 87.5-97% when entire stomach is examined
- NCI study of 128 patients undergoing PTG: 16 with HLBC, 19 with HDGC, and 93 mixed
  - Occult SRCC found in 94% with HLBC, 95% with HDGC, and 89% with mixed
- Development of SRCC foci occurs early in life, perhaps teens
- Vast majority of SRCC foci will never become a clinically significant cancer

Gamble LA et al. JAMA Surg 2021:157:1

Given the almost universal prevalence of SRCC in CDH1 carriers, we postulate that rather than maximizing detection of all SRCC, the goal of surveillance should be identifying features that predict the presence of > T1a lesions and detecting these lesions at the earliest possible stage. This strategy would represent a paradigm shift from endoscopic surveillance to this point, which sought to maximize detection of endoscopically invisible or subtly visible T1a lesions.

JNCCN review article in press

Prophylactic Total Gastrectomy

JAMA Surgery | Original Investigation

Indications for Total Gastrectomy in *CDH1* Mutation Carriers and Outcomes of Risk-Reducing Minimally Invasive and Open Gastrectomies

Elvira L. Vos, MD, PhD; Erin E. Salo-Mullen, MS, MPH, CGC; Laura H. Tang, MD, PhD; Mark Schattner, MD; Sam S. Yoon, MD; Hans Gerdes, MD; Arnold J. Markowitz, MD; Diana Mandelker, MD, PhD; Yelena Janjigian, MD; Kenneth Offitt, MD; Daniel G. Coit, MD; Zsofia K. Stadler, MD; Vivian E. Strong, MD

Vos EL et al. JAMA Surgery 2020:155:1051

- 101 prophylactic total gastrectomies
  - Median age 42 (range 17-70)
  - 68 female, 33 male
- Microscopic foci DGC on preop EGD in 23 pts
- Foci SRCC in PTG in 88 pts
  - T1a in 86, T1b in 2
- All lymph nodes negative
- No recurrences after median FU 18 months

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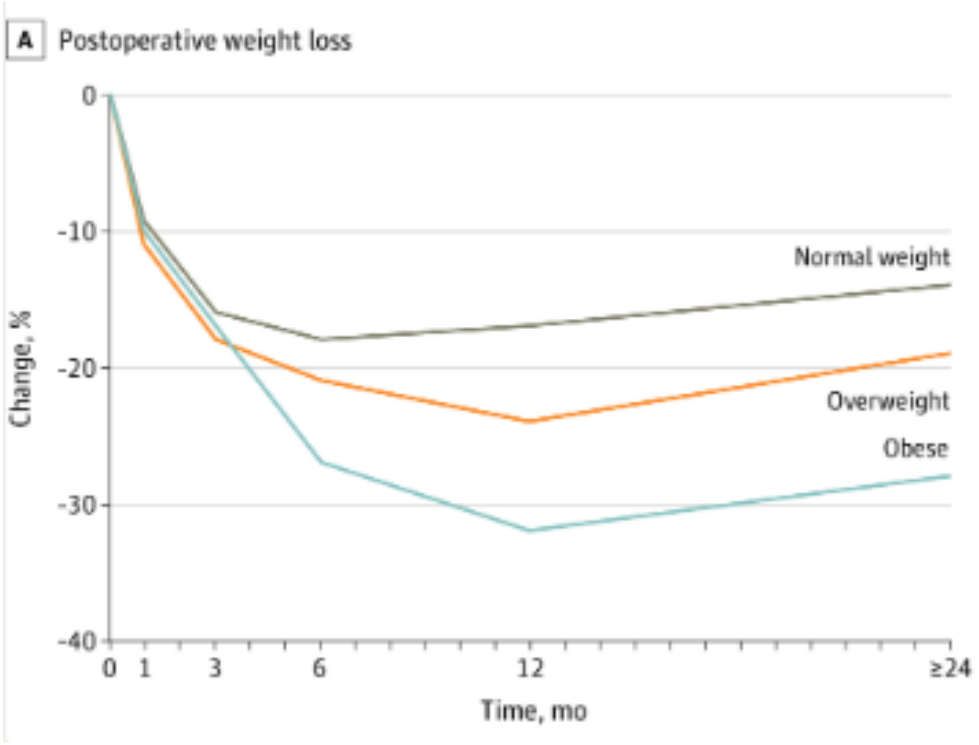
Vos EL et al. JAMA Surgery 2020:155:1051

- Early postoperative complications (<30 days)
  - Major 16%, minor 12%
  - 1 death
  - Anastomotic leak 6%
- Late complications (1-3 months)
  - Stricture requiring dilation 15%
  - Hernia repair 4%
- Weight loss
  - Median 20%



Hereditary diffuse gastric cancer: cancer risk and the personal cost of preventive surgery

P. Kaurah[1,2] · A. Talhouk[3] · A. MacMillan[4] · I. Lewis[4] · K. Chelcun-Schreiber[5] · S. S. Yoon[6] · D. Huntsman[1,3]

Familial Cancer 2019:18:5429

- 52 pts undergoing PTG between 2004-2013
  - 11 hospitals, 14 surgeons
- Median weight 146 lbs (range 101-308)
  - Median weight loss 24 lbs (range 0-101)
- 23 pts (44%) had significant complications within 6 months
  - Anastomotic leak (n=2) and/or stricture (n=12)
  - Obstruction(n=3)
- Quality of life
  - Overall EORTC QLQ-C30 mean 70.6 – better than general population
  - Depression – 6% severe
  - Satisfaction with surgery – 6% not satisfied

Short and long-term outcomes of prophylactic total gastrectomy in 54 consecutive individuals with germline pathogenic mutations in the *CDH1* gene

Yoon SS et al. J Surg Oncol 2022:126:1413

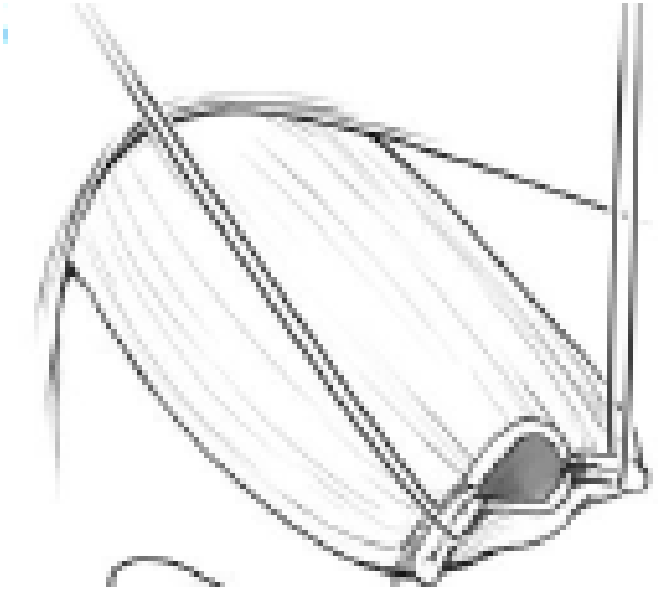
- 54 patients
  - Median age 41 (range 17-70)
  - 35 female, 19 male
- Microscopic foci DGC on preop EGD in 8 pts (15%)
- Foci DGC in PTG in 52 pts (96%)
  - All Tis or T1a
- All lymph nodes negative

J Gastrointest Surg
DOI 10.1007/s11605-016-3326-5

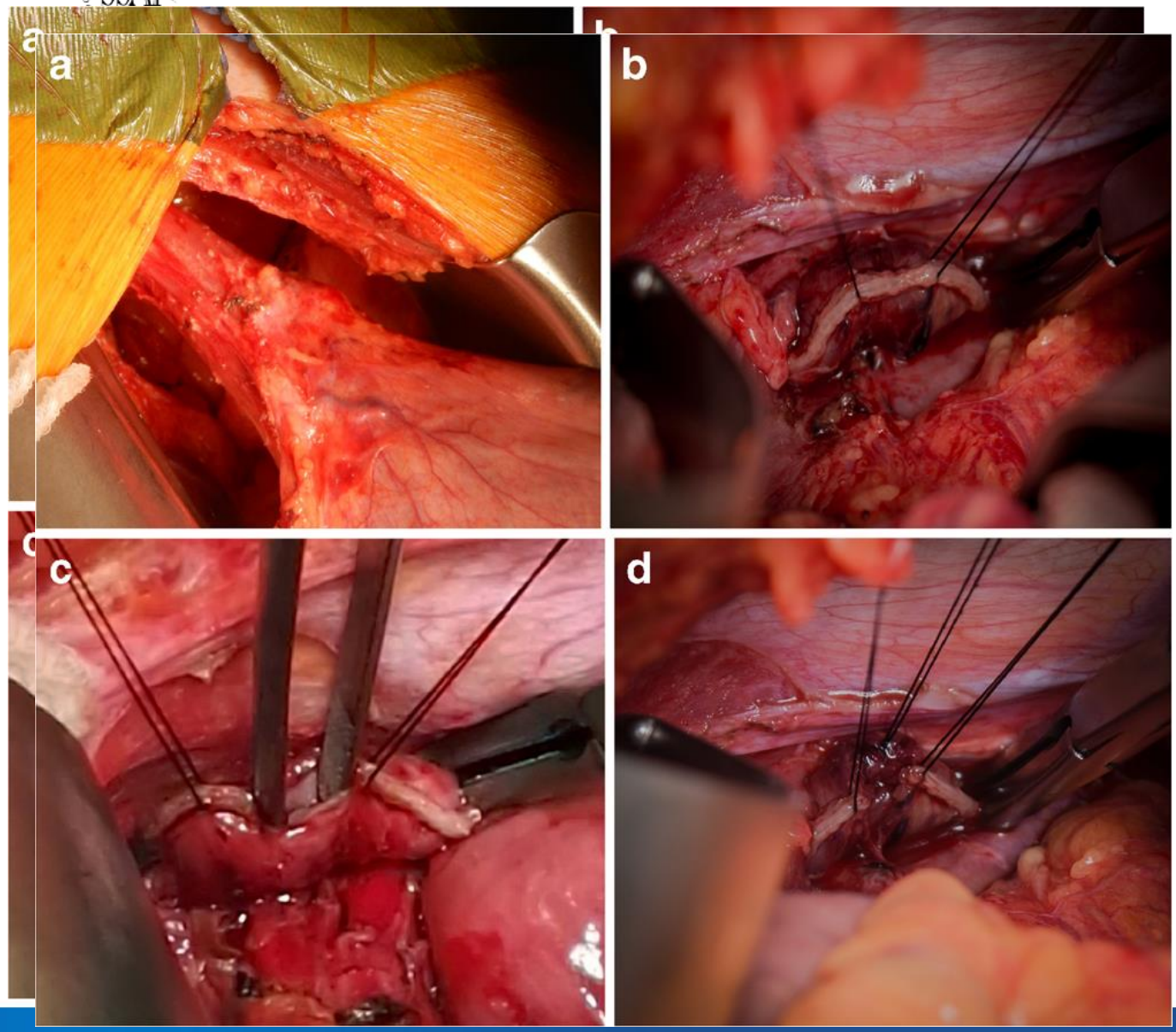
HOW I DO IT

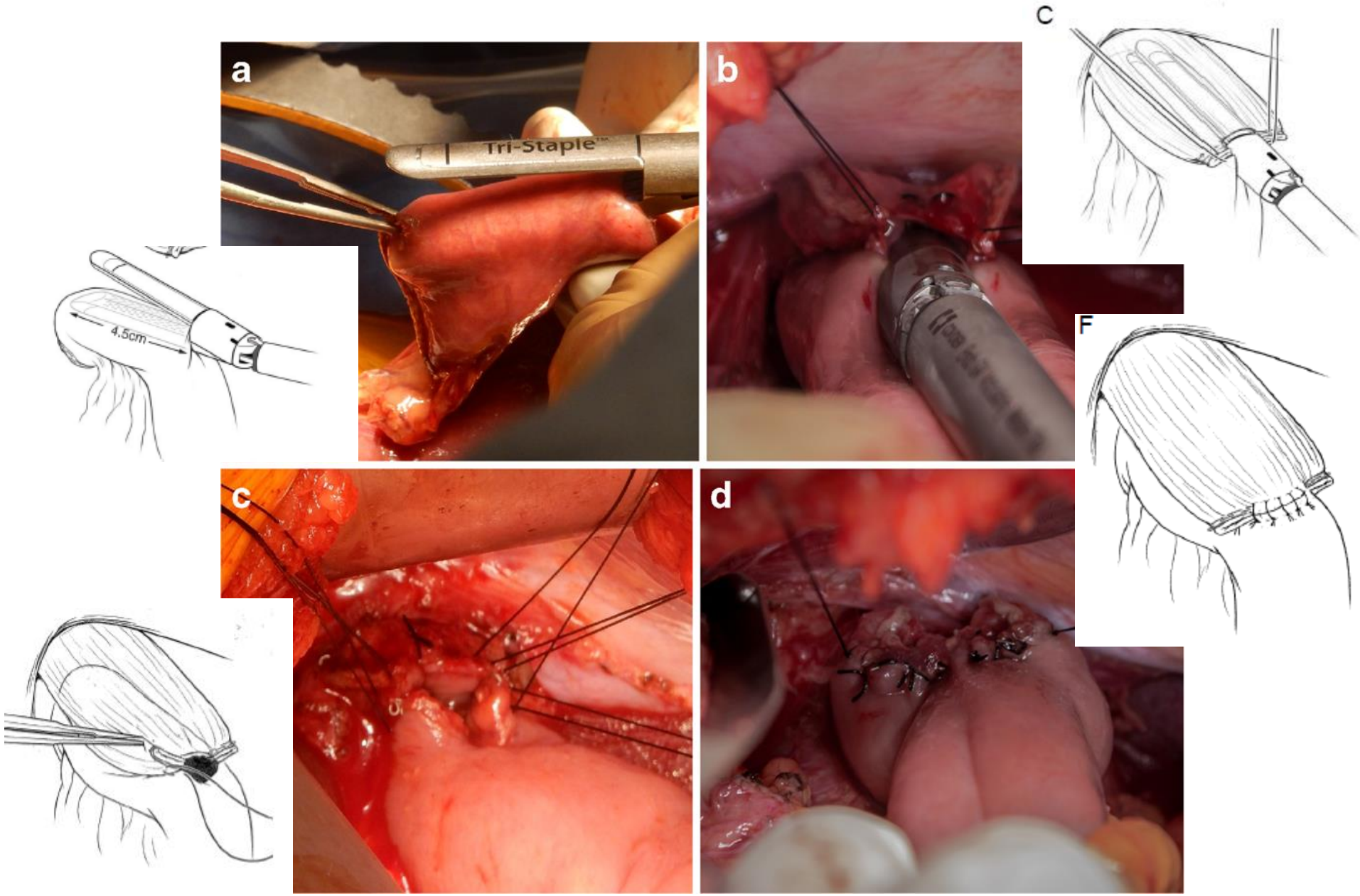
Linear-Stapled Side-to-Side Esophagojejunostomy with Hand-Sewn Closure of the Common Enterotomy After Prophylactic and Therapeutic Total Gastrectomy

Kevin K. Chang[1] · Madhukar S. Patel[2] · Sam S. Yoon[1,3]



J Gastrointest Surg 2017:21:712-22




a
Tri-Staple™
4.5cm
b
C
F
c
d

Prophylactic Total Gastrectomy Short Outcomes in 54 Patients

- Hospital stay median 7 days (range 6-12 days)
- Major complications within 30 days, 5 pts (9%)
  - 1 PE, 1 pancreatitis, 1 UTI, 2 cellulitis
  - No anastomotic leaks or strictures
- Median weight loss median 19%, max 39%

Yoon SS et al. J Surg Oncol 2022:126:1413

Prophylactic Total Gastrectomy Long-Term Outcomes in 20 Patients

- Late complications requiring invasive procedure, 5 pts (7%)
  - 1 feeding tube
  - 1 small bowel intussusception
  - 2 hernias
- Long-term weight loss median 15%
- CDC Health Related QOL median 2 (very good)
  - Range 1 (excellent) to 3 (good)
  - No patient responded 4 (fair) or 5 (poor)
- Meal size compared to before PTG median 75% (range 25-100%)
- Nearly all pts had problems with certain foods or liquids
- All pts would have PTG again

Yoon SS et al. J Surg Oncol 2022:126:1413

Summary

- Individuals with germline *CDH1* mutation are at risk of developing diffuse gastric cancer and lobular breast cancer
  - Risk calculations have changed significantly over time
- Clinical importance of microscopic foci of SRCC is debatable
  - Nearly all prophylactic total gastrectomy specimens contain foci of early diffuse gastric cancer
- Endoscopic screening may or may not detect a cancer at an early stage
  - Requires endoscopist experienced in detecting early SRCC
- Prophylactic total gastrectomy is definitive treatment
  - Risk of complications
  - Long-term sequelae on eating and nutrition
  - Long-term quality of life is generally very good


Thank You