Early-Onset Gastric Cancer

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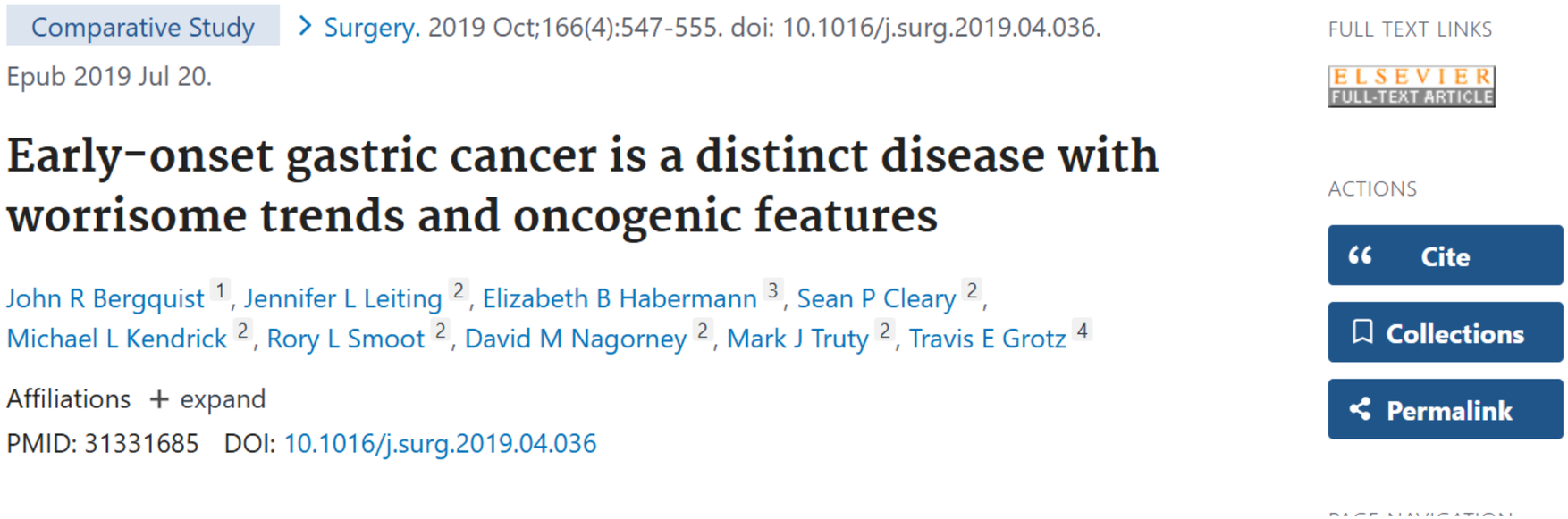
Gastric cancer (GC) is the fifth most frequently diagnosed cancer.

GC is divided into early-onset gastric cancer (EOGC—up to 45 years of age) and conventional GC (older than 45).

EOGC constitutes approximately 10% of all GCs.



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Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features

John R Bergquist [1], Jennifer L Leiting [2], Elizabeth B Habermann [3], Sean P Cleary [2], Michael L Kendrick [2], Rory L Smoot [2], David M Nagorney [2], Mark J Truty [2], Travis E Grotz [4]

Affiliations + expand

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Why early onset is a challenge

Vague symptoms

Early symptoms are often non-specific and easily overlooked, making initial detection difficult.

Delayed diagnosis

The combination of vague symptoms and young patient age often leads to significant diagnostic delays.

Unique characteristics

Poorer prognosis, higher rate of poorly differentiated or diffuse-type tumors.

Hereditary Factors of Gastric Cancer

Majority are sporadic

Most gastric cancers occur without hereditary factors

10% show familial connection

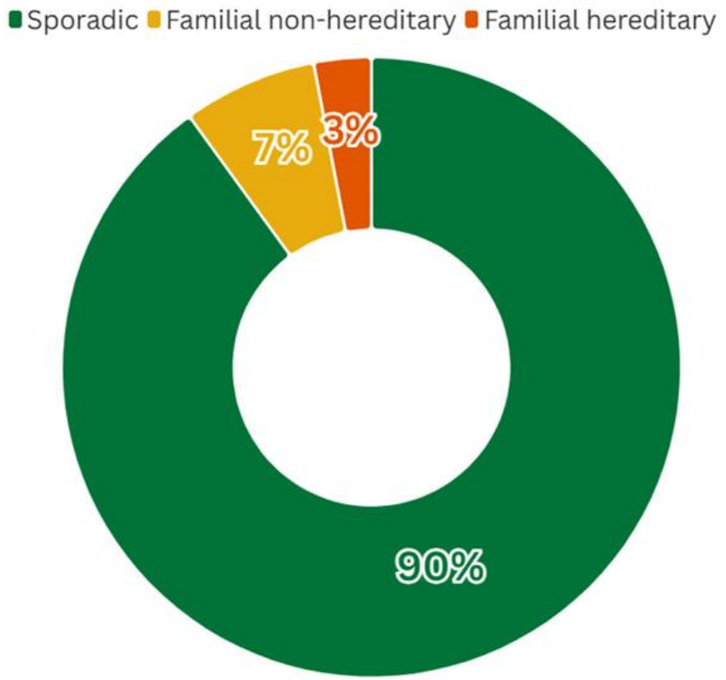
A notable portion demonstrates family clustering

1-3% truly hereditary

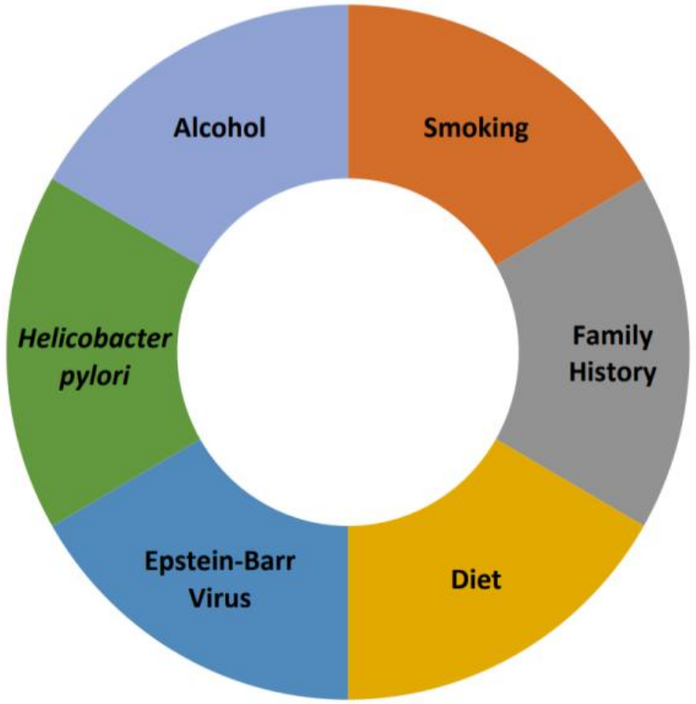
Only a small fraction are caused by inherited genetic mutations

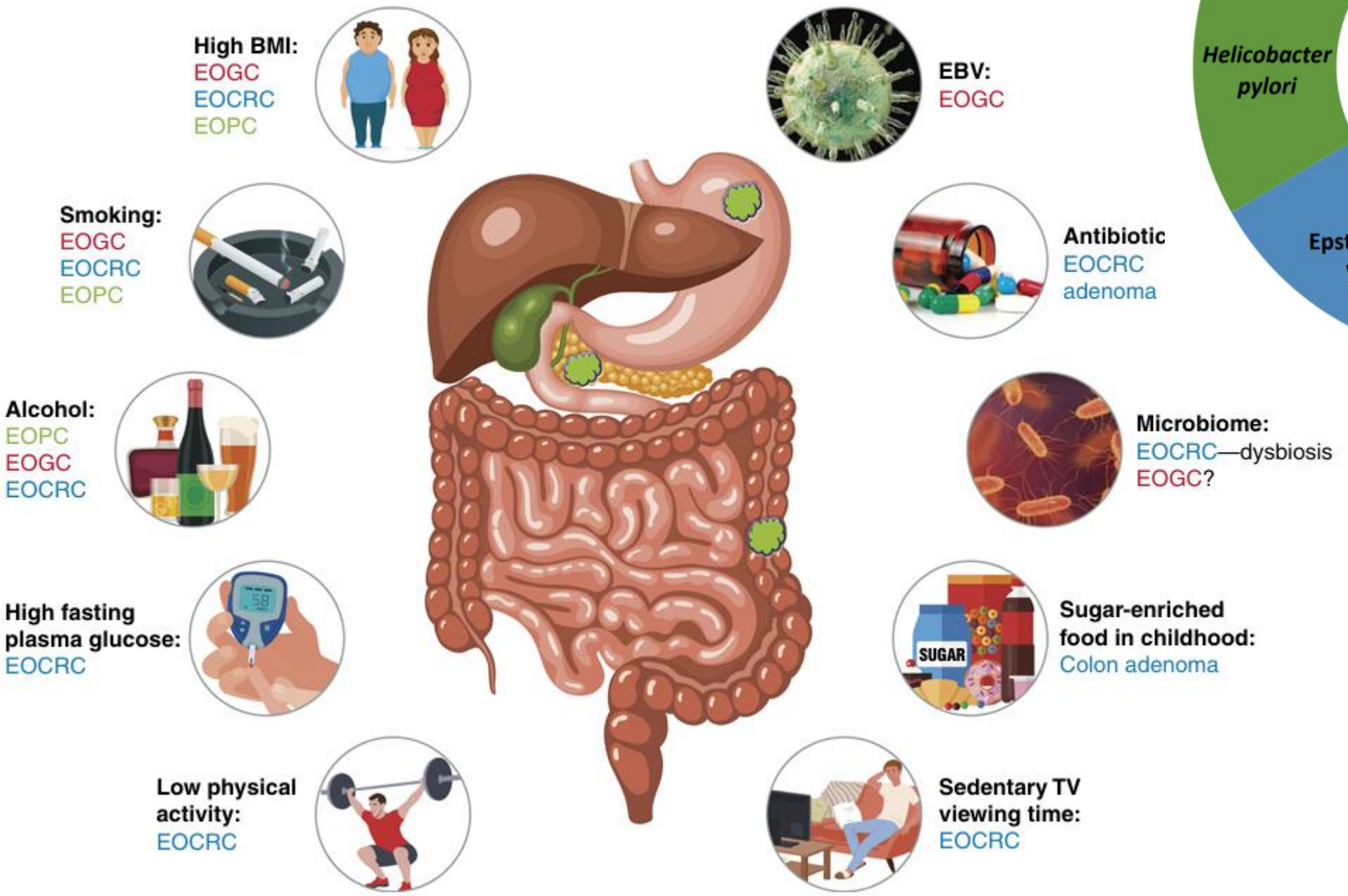
Specific characteristics guiding genetic testing:

- Young age < 50
- Family history
- Diffuse-type histology



Risk factors for GC development





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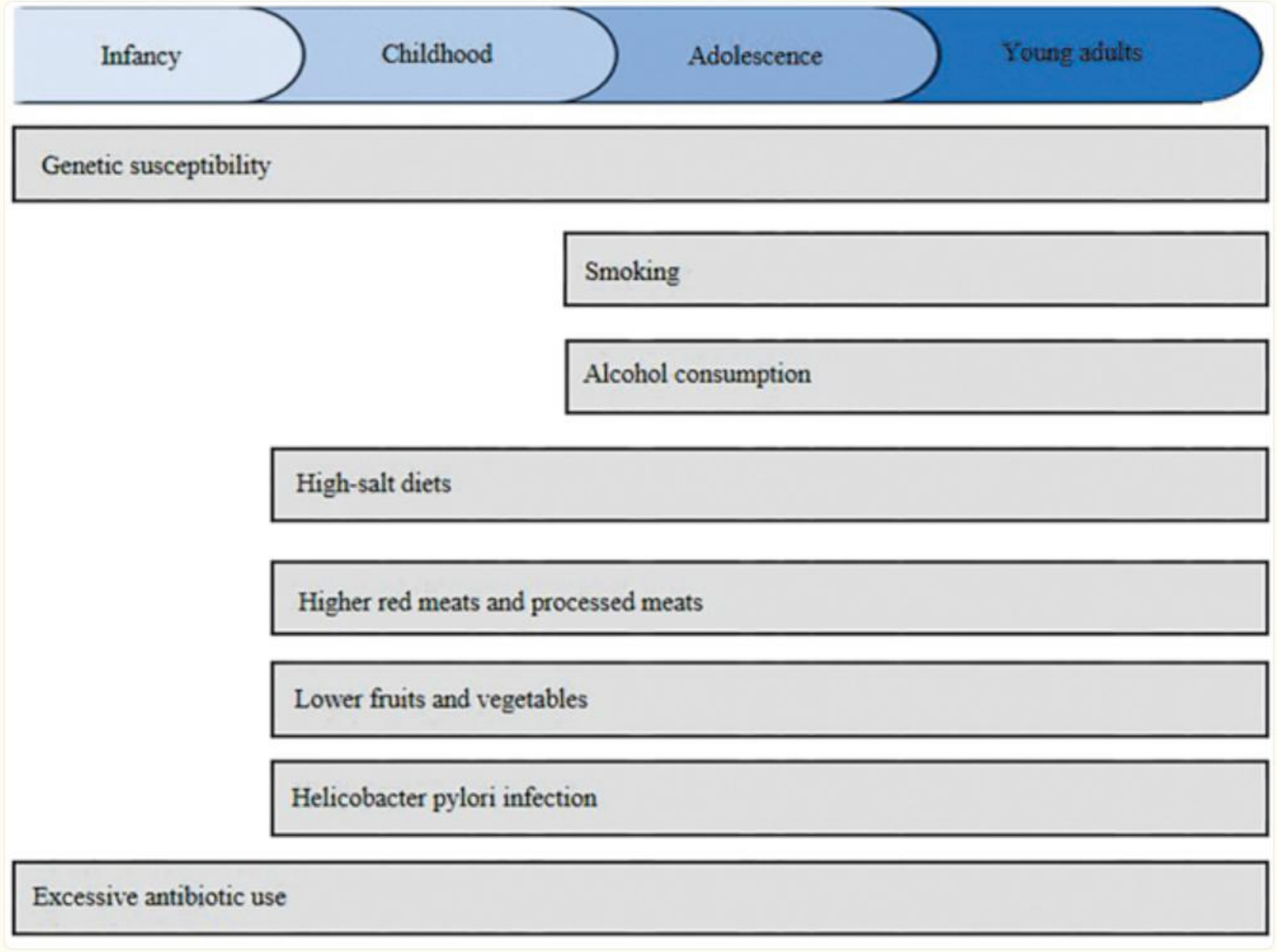
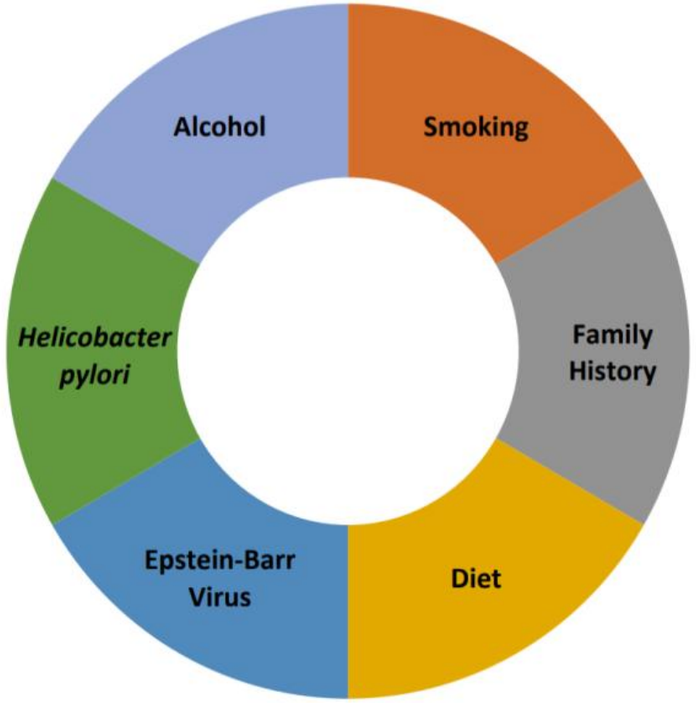




Types of familial gastric cancer

Hereditary diffuse gastric cancer (HDGC)

The most notable familial GC is HDGC, caused by mutations in the gene coding E-cadherin (CDH1).

Familial intestinal gastric cancer (FIGC)

A distinct hereditary form affecting intestinal-type gastric cancer development.

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

A rare hereditary syndrome characterized by fundic gland polyps and increased cancer risk.

Hereditary diffuse gastric cancer (HDGC)

Germline mutations in the CDH1 gene

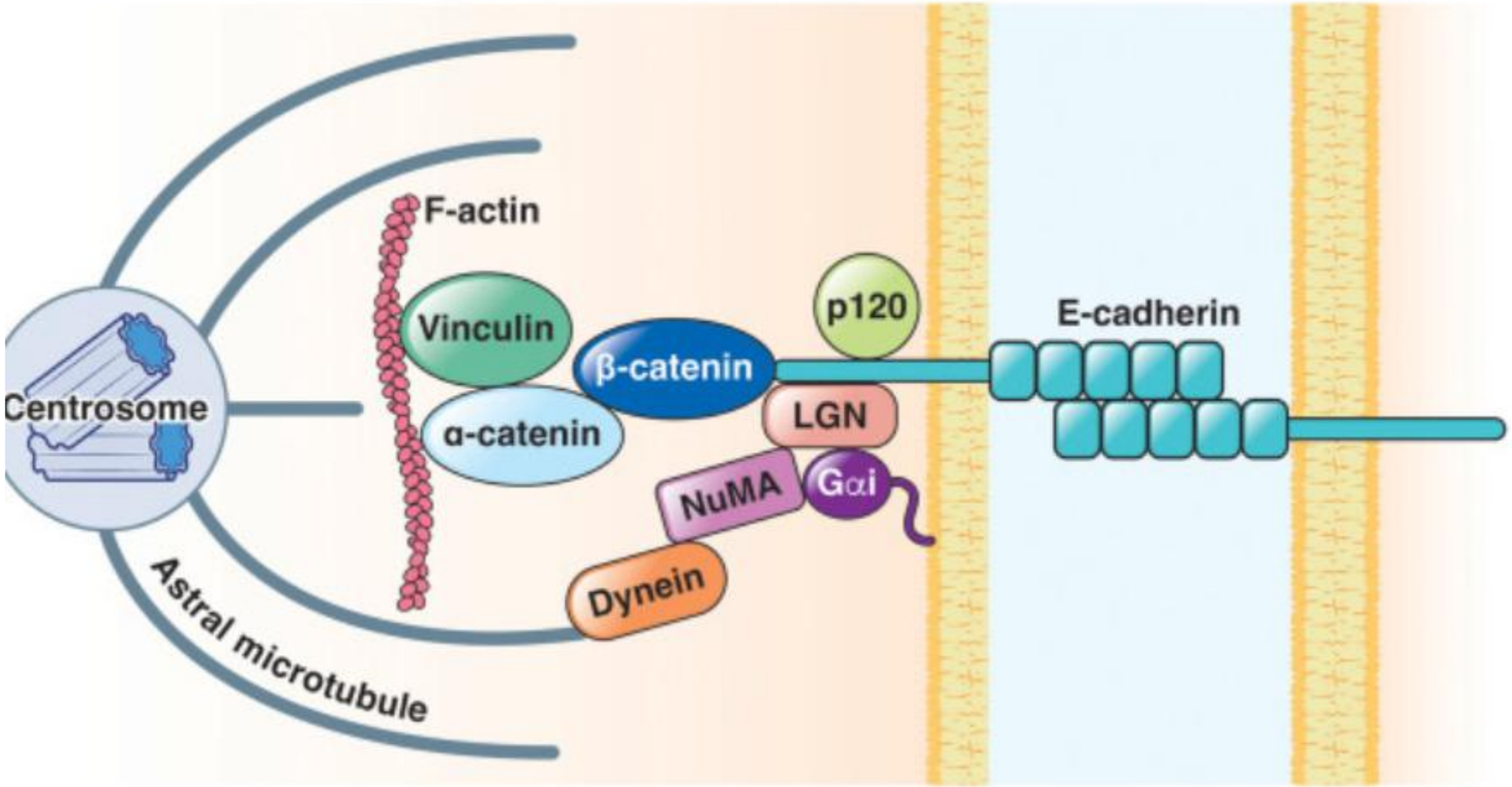
- Identified in approximately 30–50% of cases
- Less frequently in CTNNA1

Cancer types associated with HDGC

- **Stomach cancer:** diffuse gastric cancer (DGC)
- **Breast cancer:** lobular breast cancer (LBC)

The most noticeable familial GC is HDGC, a cancer induced by modifications in the gene coding E-cadherin (CDH1)

Hereditary diffuse gastric cancer (HDGC)



Family criteria (1st or 2nd degree blood relatives of each other)

- ≥2 cases of gastric cancer in family regardless of age, with at least one DGC
- ≥1 case of DGC any age and ≥1 case of LBC <70yrs in different family members
- ≥2 cases of LBC in family members <50yrs

Individual criteria

- DGC <50yrs
- DGC at any age in individuals of Māori ethnicity
- DGC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate
- History of DGC and LBC, both diagnosed <70yrs
- Bilateral LBC (cancer in both breasts), diagnosed <70yrs
- Gastric in situ signet ring cells and/or pagetoid spread (bottom to top) of signet ring cells in individuals <50yrs

Familial intestinal gastric cancer (FIGC)

•**Inheritance:** It is an inherited cancer syndrome, believed to have an autosomal dominant inheritance pattern.

•**Tumor type:** It is specifically associated with intestinal-type gastric cancer, which develops in the mucus-producing cells of the stomach lining.

•**Genetic cause:** The exact gene responsible is not yet known.

•**Diagnosis:** It is diagnosed based on clinical criteria, such as having multiple family members with intestinal-type gastric cancer, with specific age-of-onset and relationship requirements depending on the cancer incidence in the region.

•**Exclusion:** It excludes families with gastric polyposis or those with a known mutation like those associated with

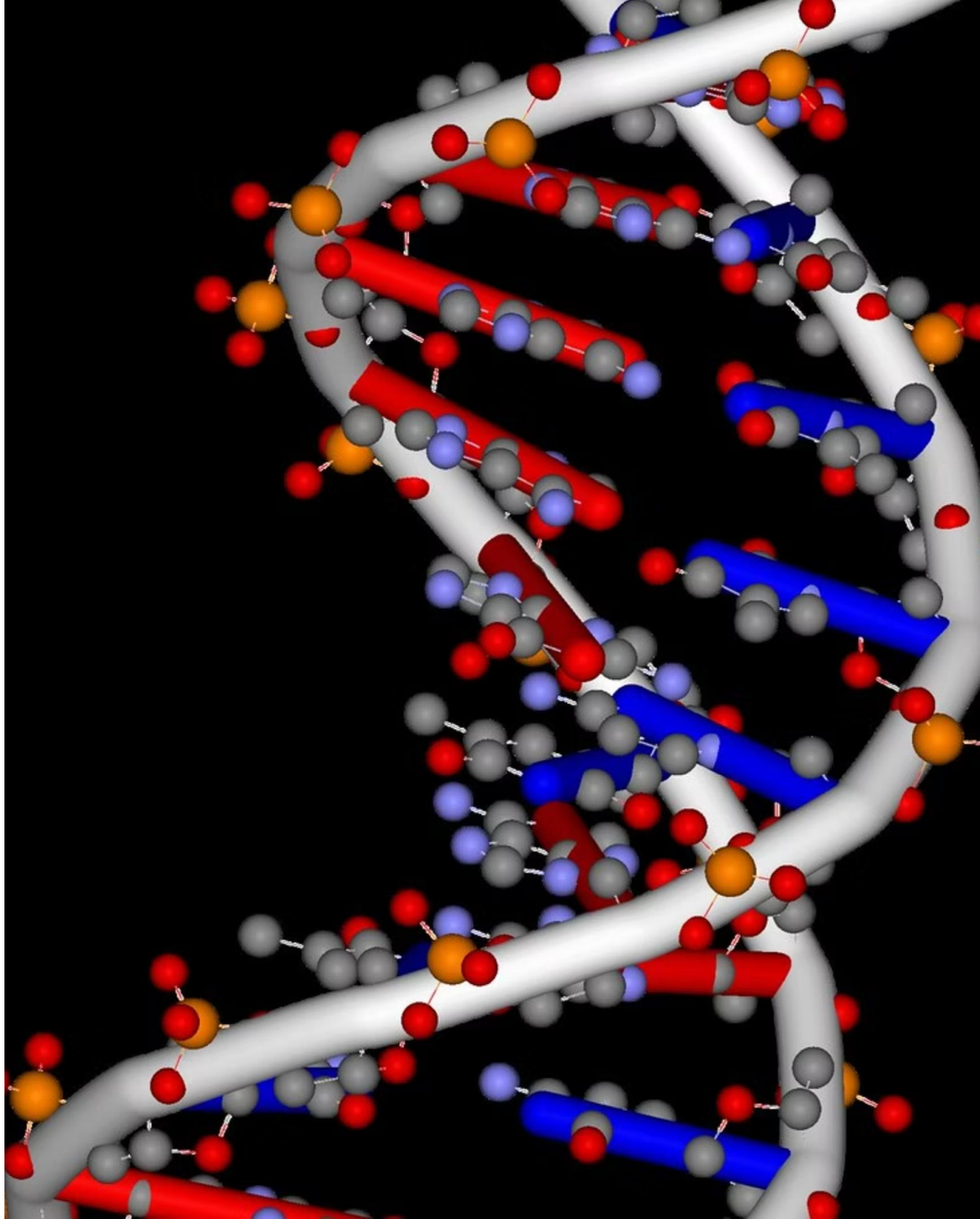


Table 1. Main hereditary syndromes associated with increased colorectal, pancreatic, and/or gastric cancer risk

	Germline mutation–associated gene(s)	Associated phenotype and increased risk of GI tumor onset
Lynch syndrome	*MLH1/MSH2/PMS2/MSH6*	Increased risk of colorectal cancer: 52%–82% lifetime risk (31) Pancreatic cancer: 4% by age of 70 (32, 33) Gastric cancer: 13% by age of 75 (34)
FAP	*APC*	>100 adenomatous polyps in young age, increased risk of colorectal and duodenal cancers: 100% risk by age of 50 (31)
aFAP		10–100 adenomatous polyps, colorectal: later onset than FAP: 70% risk by age of 80 (31) Gastric cancer: risk depending on the region, not increased in United States, but 3–4 times increased in Japan (35)
MAP	*MUTYH*	Colorectal cancer: 63% risk by age of 60 (31)
Hereditary pancreatitis	*PRSS1*, *CTRC*, *CFTR*	Pancreatic cancer: 26-fold increased risk, 10% by the age of 50 (31)
Hereditary breast and ovarian cancers	*BRCA1*, *BRCA2*	Pancreatic: 5%–10% lifetime risk (36)
HDGC	*CDH1*, *CTNAA1*, *MAP3K6*	Gastric cancer: 70% (males), 56% (females) by the age of 80 (37)
Li–Fraumeni syndrome	*TP53*	Gastric cancer: 4%–7% (29% before the age of 30; ref. 37)
PJS	*STK11/LKB1*	Colorectal cancer: 39% lifetime risk (39) Pancreatic cancer: 32% by the age of 70 (40) Gastric cancer: risk increased, no larger series published
FAMMM syndrome	*CDKN2A*	Pancreatic cancer: 17% by age of 70 (41)
FA	FA genes group	Pancreatic cancer: similar to *BRCA2* mutations (41)
GAPPS	*APC* promoter 1B	Gastric cancer: numerous polyps in gastric body and high risk (not quantified in literature) of malignant transformation

Abbreviations: aFAP, attenuated FAP; FA, Fanconi anemia; FAMMM, familial atypical multiple mole melanoma; MAP, MYH-associated polyposis.

Clinico-pathological and molecular-genetic differences between early-onset and conventional gastric cancers

Conventional gastric cancer	Early-onset gastric cancer	Ref.
Equally common in male and females	More common in females	[13,28,30,31]
Intestinal type cancer more common	Diffuse type cancer more common	[13,28]
Usually unifocal	Often multifocal	[32,33]
Often preceded by intestinal metaplasia	No intestinal metaplasia	[13,28]
Microsatellite Instability in 15%-20%	Lack of MSI	[24,29,41-43]
Commonly find loss of heterozygosity	Infrequent loss of heterozygosity	[24]
COX2 overexpression in 66%	COX2 overexpression in 10%	[46]
Loss of TFF1 expression in 73%	Loss of TFF1 expression in 39%	[46]
Loss of RUNX3 gene	No loss of RUNX3	[58-61]
Widespread gains throughout genome	Gains at chromosomes 17q, 19q and 20q	[40]
Distinct gene clusters on hierarchical analysis	Distinct gene clusters on hierarchical analysis	[39]
Infrequent LMW isoforms of cyclin E	Frequent LMW isoforms of cyclin E	[52]
CD44v6 expression	CD44v6 more commonly expressed	[57]
Usually no family history	10% with a family history	[13]

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Screening for Gastric Cancer

> Only a few countries with high GC prevalence have organized screening programs

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Table 1. Risk Factors That Should Prompt Consideration of a Personalized Approach to Screening for Gastric Cancer in the United States Among Individuals 45 Years and Older

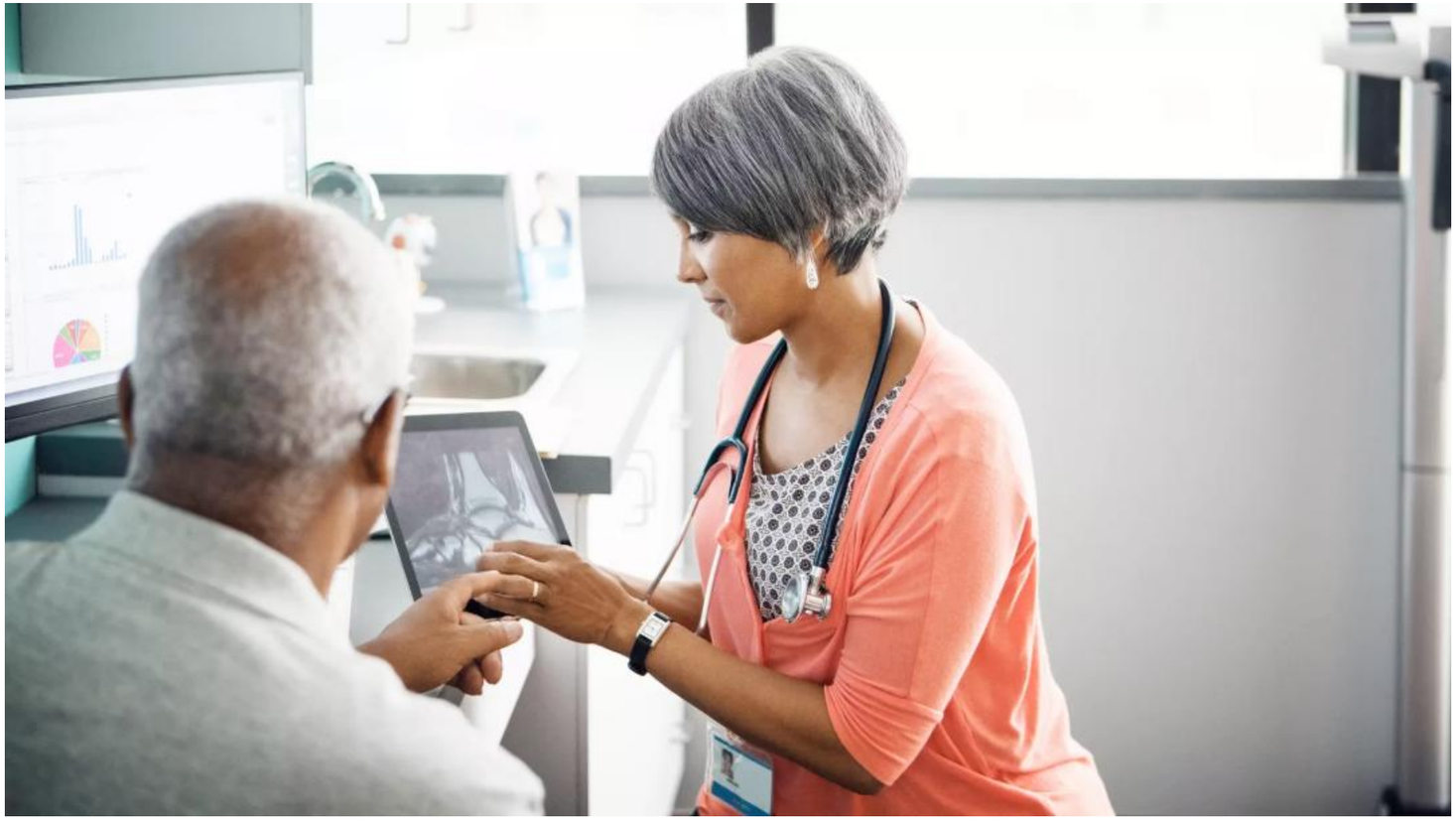
Risk factors
Early-generation immigrants from moderate to high incidence GC regions (defined as GC incidence ≥10–12 per 100,000 people; includes Eastern Europe, Andean Latin America, and East Asia)[a]
Family history of GC in a first-degree relative (to start 10 y earlier than the youngest affected relative)
Non-White racial and ethnic groups with established moderate to high incidence GC[a]
Personal history of chronic *Helicobacter pylori* infection and at least 1 of the following: • History of regularly smoking tobacco (>20 pack-years) • Chronic consumption of high-salt diet, red meat, processed meats, and foods • Individuals living under persistent poverty in the United States[b]
Certain hereditary GI polyposis syndromes and hereditary cancer syndromes

Screening for Gastric Cancer

Endoscopy for screening

Best test for screening or surveillance in high-risk individuals

Important consideration:
Up to 10% of precancerous lesions may be missed in the three years before GC diagnosis



Screening for Gastric Cancer

Biopsy protocol

In suspected gastric atrophy with or without intestinal metaplasia, biopsies should follow systematic protocols such as the updated Sydney System

01

Minimum 5 biopsies

With separate labeling for samples from different stomach regions

02

Suspicious areas

Described and biopsied separately

Endoscopic detection challenges

- Gastric intestinal metaplasia (GIM) and dysplasia can be detected but often missed due to lack of endoscopist training
- Need for improved training, especially in the US
- AI tools promising but not yet recommended routinely

H. pylori eradication

Essential as an adjunct to screening and surveillance for primary and secondary prevention

Screening for H. pylori in adult household members of infected individuals (familial-based testing) recommended

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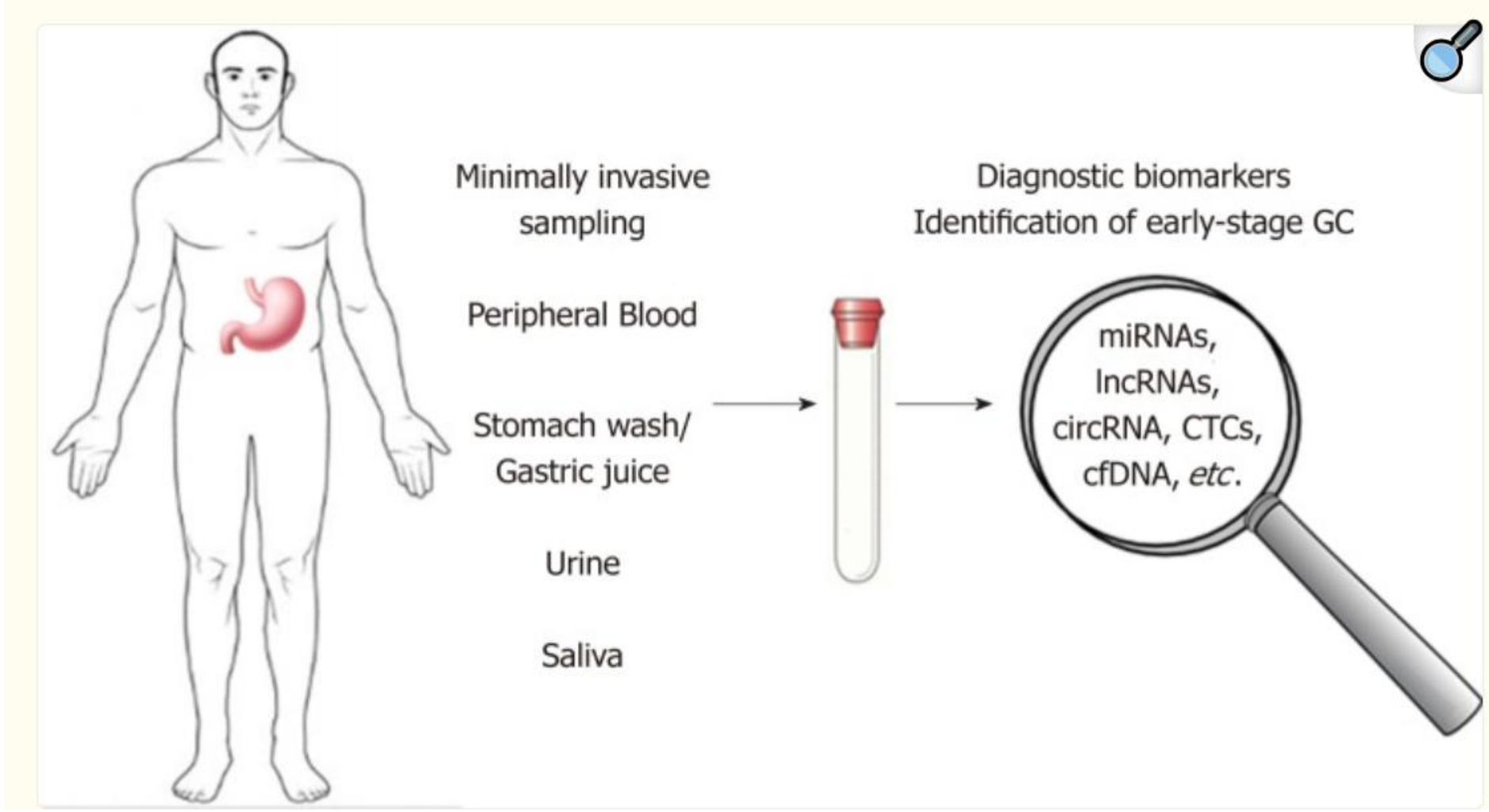
Biomarkers

- CEA
- Ca19-9
- PGI/PGII ratio
- Ca 12-5
- Ca 72-4



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Lifestyle and prevention

Lifestyle modification

Lifestyle plays an important role in carcinogenesis, requiring strong focus on modification

H. pylori eradication

Encouragement of H. pylori eradication when possible

Surveillance

Careful surveillance of precancerous conditions and endoscopic vigilance are necessary

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