



Genetics and GE cancers

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Disclosures

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Agenda

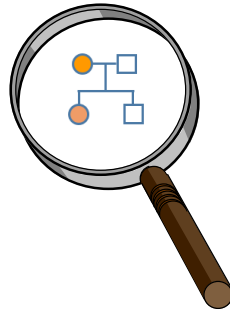
- Clues to inherited cancers
- Overview of a Cancer Genetics appointment
- Inherited syndromes with gastric cancer
- Inherited syndromes with esophageal cancer

Most esophageal and gastric cancers are not inherited

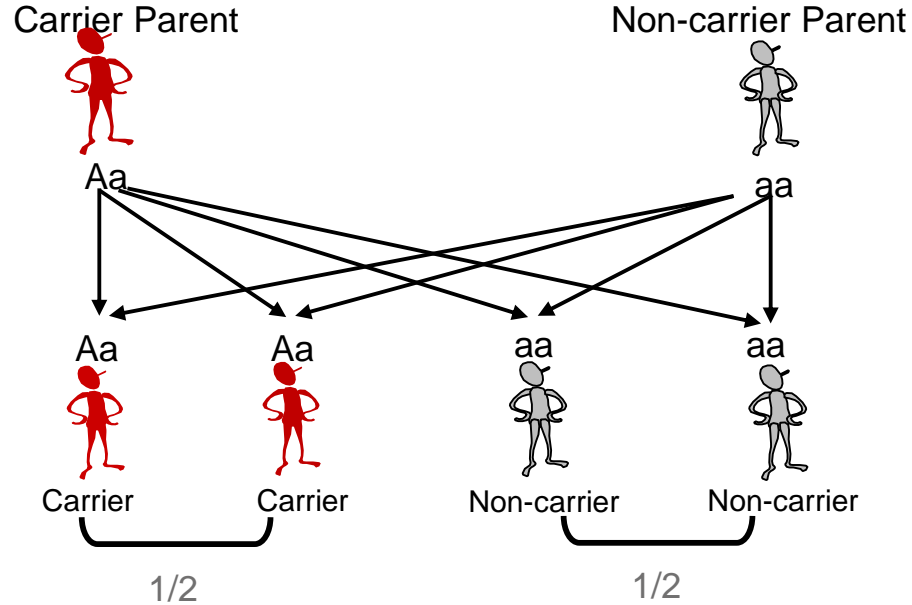
- Gastric cancer
 - Estimated 1-3% are related to inherited syndromes
 - Cavatorta et al. Epidemiology of gastric cancer and risk factors. Acta Biomed 2018.
- Esophageal cancer
 - Less than 1% (probably less than 0.1%) are related to inherited syndromes
- Familial clustering can be related to combination of multiple low risk genes, lifestyle factors, *H.pylori* and other factors

Clues to inherited cancers

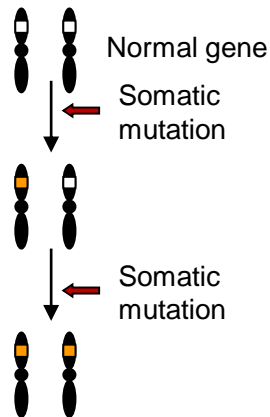
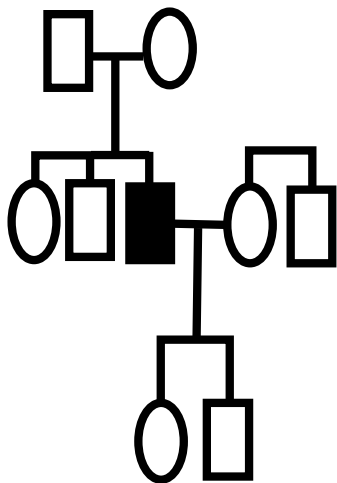
- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple cancers at the same time
- Multiple rare cancers in a family
- Evidence of autosomal dominant transmission



Autosomal Dominant Inheritance

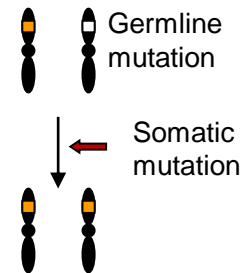
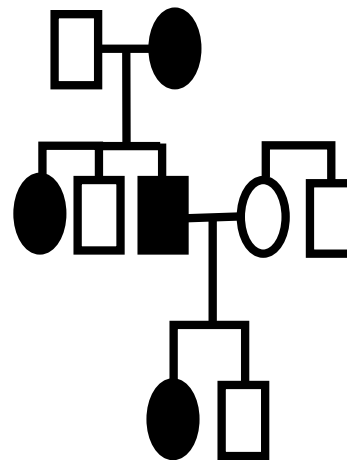


Sporadic



- Later age at onset (60s or 70s)
- Little or no family history of cancer
- Single or unilateral tumors

Inherited



- Early age at onset (<50)
- Multiple primary tumors
- Multiple generations with cancer
- Clustering of certain cancers (i.e. breast/ovarian)

Genetic counseling

Cancer genetics appointments are about 90 min

They include:

1. Review of clinical history (personal and family)
2. Consideration of most likely diagnosis
3. Discussion of pros/cons of genetic testing
4. Ordering and drawing of genetic testing if indicated and patient provides informed consent

***Along with knowledge of insurance and lab rules**

5. Most importantly post-result counseling

Genetic counseling

Benefits of genetic counseling and testing:

- Accurate counseling on risks for future cancers
 - Both another cancer in same organ as well as risk of other cancers
- Discuss potential results prior to testing
- **Predictive testing of at-risk family members**

Genetic testing

There are many myths about genetic testing but this is now very common and very easy to obtain!

- Can be done from blood, saliva or uncommonly from skin culture (if history of BMT)
- Cost – this is very commonly covered by insurance. If not, the out of pocket price is usually \$250 or less (if ordered through GC with lab knowledge)
 - Medicare/Medicaid free through many labs
 - Family testing free after a positive result for many labs!
- GINA is an act of congress that prohibits genetic discrimination
 - Protects from employment and health insurance discrimination based on genetic testing
 - Life insurance is not protected

Genetic testing

There are many myths about genetic testing but this is now very common and very easy to obtain!

- We very often do “Panel Testing”, where we test multiple genes at the same time (often 47 or more)
 - Many genes all for same cost with current technology
- If a gene mutation is known in family, we will often only test for that gene in relatives unless there is concern for 2 syndromes in family
 - This is free at many labs for 90 days after initial test
 - If test was previous, can be done now for as little as \$50

Genetic testing

There are many myths about genetic testing but this is now very common and very easy to obtain!

- Genetic testing results can also help determine treatment options
 - Lynch syndrome patients respond well to immunotherapy
 - BRCA patients respond to PARP inhibitors

Who should be seen in Genetics?

- Best candidate for testing is the person most likely to be affected
 - Meaning the person with cancer or the person in family at cancer at youngest age
 - If that person is unavailable or unwilling, we would then prefer to see closest relative to them
- An unaffected patient cannot be a “true negative” if they are only person to test in family

When should Genetics referral occur with Gastric and esophageal cancers?

Gastric cancer

- ≥ 2 cases of gastric cancer, one dx at age < 50 in close relatives
- ≥ 3 cases of gastric cancer in close relatives
- Diffuse gastric cancer dx at age < 40
- Diffuse gastric cancer and lobular breast cancer in the same person
- Diffuse gastric cancer in one relative and lobular breast cancer in another, one dx at age < 50
- Gastric cancer and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives

Esophageal – No formal recommendations, but I would add:

- Multiple cases of squamous cell esophageal cancers in a family

Hereditary Diffuse Gastric Cancer (due to CDH1 mutation)

Characterized by diffuse gastric cancer (specific finding on pathology, rare)

- High risk for diffuse gastric cancer (70% for men; 56% for women)
- Increased for lobular breast cancer (42%) for affected women
- Screening endoscopy or ultrasound is not beneficial
- Prophylactic gastrectomy (stomach removal) recommended at 20-30 yo

Hereditary Diffuse Gastric Cancer (due to CDH1 mutation)

Recommend testing for CDH1 mutation if:

- 2 Cases of Gastric cancer in family, with 1 confirmed diffuse
 - Diffuse gastric cancer at < 40 yo
 - Diffuse gastric cancer and lobular breast cancer in family, with at least one < 50 yo
-
- Consider testing if:
 - 2 or more lobular breast cancer in person or family
 - Diffuse gastric cancer and cleft lip/palate

Case - HDGC

52-year-old female with gastric cancer diagnosed at age 51

Pathology: Poorly differentiated carcinoma with signet ring cell features and a diffuse infiltrative pattern

Foundation Medicine tumor sequencing ordered for treatment direction

- 2 *CDH1* mutations were identified in her gastric tumor

Case 2: Tumor Sequencing Results

PATIENT RESULTS

3 genomic alterations

0 therapies associated with potential clinical benefit

0 therapies associated with lack of response

0 clinical trials

TUMOR TYPE: STOMACH ADENOCARCINOMA
(NOS)

Genomic Alterations Identified†

ARID1A Y803*

CDH1 C688fs*1, splice site 531+1G>A

Case 2: HDGC

Genetic testing done and showed:

Specific Site Analysis of CDH1

RESULTS

CDH1 SPECIFIC SITE c.2064_2065delTG Pathogenic Mutation: Detected

INTERPRETATION

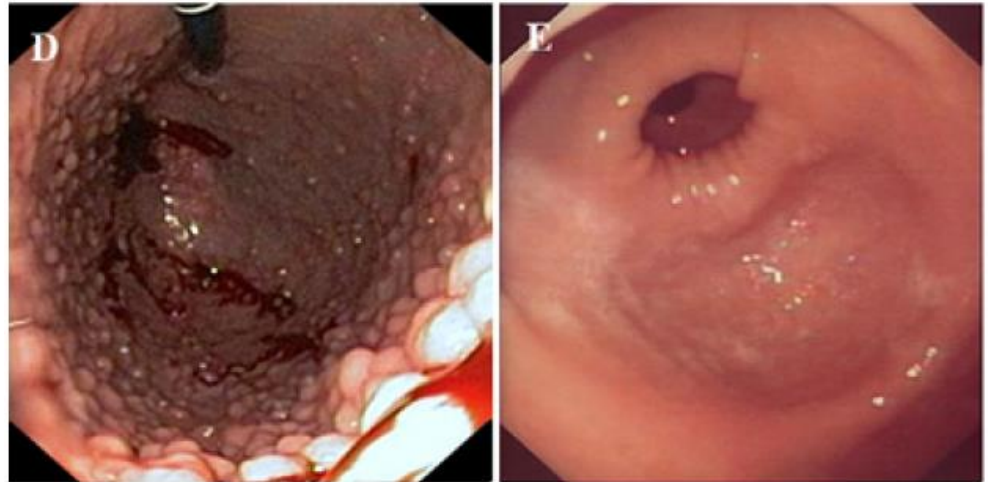
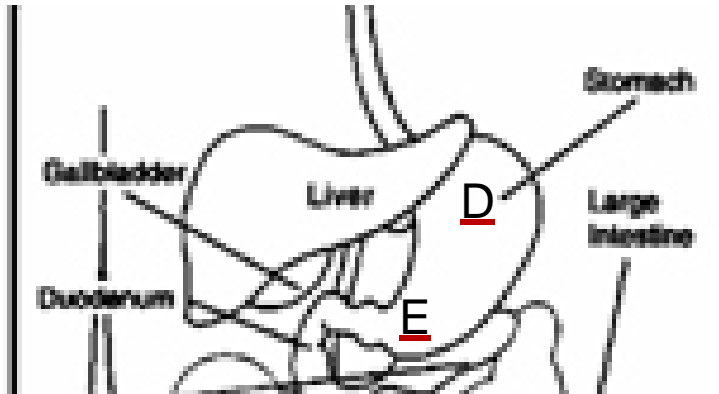
This individual is heterozygous for the c.2064_2065delTG pathogenic mutation in the *CDH1* gene, which was previously identified in

This allowed family members to be tested and determine their risk and start discussing endoscopy and prophylactic surgery

GAPPS (Gastric adenocarcinoma and Proximal Polyposis of the stomach)

GAPPS

- Newly described in 2012
- Still very rare even with availability of clinical testing
- >100 proximal fundic gland polyps with sparing of antrum
- Gastric cancer risk is high



Genetics syndromes associated with gastric cancer

None of these conditions have gastric cancer as a primary finding

- Familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP)
 - Usually > 100 large intestine adenomatous polyps (at least 20)
 - Gastric cancer risk is <1%, but increasing
- Peutz Jeghers syndrome and Juvenile polyposis syndrome
 - Hamartomatous polyps in stomach and large intestine
 - PJS gastric cancer risk is 29%
 - PJS also has characteristic dark spots on lips
 - Juvenile polyposis gastric cancer risk is 20%



Genetics syndromes associated with gastric cancer

None of these conditions have gastric cancer as a primary outcome

- Lynch syndrome
 - Most common inherited cause of colon (large intestine) and endometrial (uterus) cancer
 - Gastric cancer risk varies by mutation type, range 5-16% for higher risk genes to <1% for lower risk genes
- Li Fraumeni syndrome
 - Severe cancer syndrome, often breast cancer and sarcomas at less than 30 years of age
 - Gastric cancer risk 2%

Inherited syndromes associated with gastric cancer

Syndrome	Associated gene(s)	Lifetime gastric cancer risk	Other associated cancers	Nonmalignant phenotypic features
HDGC	<i>CDH1</i> ; possibly <i>CTNNA1</i> , <i>MAP3K6</i> , and others	67%–70% (males), 56%–83% (females)	Lobular breast carcinoma	Cleft lip/palate in some families
FAP	<i>APC</i>	<1% ^a	Colorectal duodenal/ampullary, thyroid, desmoid tumors, hepatoblastoma, medulloblastoma	Colorectal (and duodenal and gastric) adenomas, gastric fundic gland polyps, osteomas, CHRPE, supernumerary teeth
GAPPS	<i>APC</i> (promoter 1B region)	Undefined, but likely higher than FAP	None known	Fundic gland polyps of the proximal stomach
Lynch syndrome	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i>	<1% to 13% ^a	Colorectal, endometrial, ovarian, urothelial, pancreatic, small-bowel, and hepatobiliary	Cutaneous sebaceous adenomas and keratoacanthomas
Li–Fraumeni syndrome	<i>TP53</i>	~5% ^a	Breast, sarcomas, lung, adrenocortical, brain (choroid plexus), leukemias, colorectal, many others	None
Peutz–Jeghers syndrome	<i>STK11</i>	~29%	Breast, pancreatic, lung, colorectal, small intestine, ovaries, testes	Hyperpigmentation of oral/genital mucosa, lips, fingers; hamartomatous polyps of GI tract, especially small bowel
Juvenile polyposis syndrome	<i>BMPR1A</i> , <i>SMAD4</i>	~21%	Colorectal and duodenal cancers	Juvenile polyps of the GI tract

Genetic causes of esophageal cancer

Tylosis

- Very rare (only a few families worldwide)
- Caused by mutations in the *RHBDF2* gene
- High risk of squamous cell esophageal cancer (> 90% in one family)
- Also very thick skin on palms of hands and soles of feet
- Recommend upper endoscopy annually starting in 20s



What are we doing at OSU Genetics?

- Universal testing of GI tumors (including gastroesophageal cancers) with IHC
 - Initial screening test for Lynch syndrome
 - Previously only done on colon and endometrial cancers

TABLE 2. Prevalence of Lynch Syndrome by Tumor Type and MSI Status

Tumor Type	Total Count	MSI-H/I	% MSI-H/I Lynch	95% CI
Gastric	211	13	15.4 (2/13)	1.9 to 45.5
Esophageal	205	16	0 (0/16)	0.0 to 20.6

Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. JCO 2018.

What are we doing at OSU Genetics?

- Reviewing all Foundation One (tumor genetic testing results) for mutation signatures suspicious for hereditary conditions

Summary

- **Most gastric and esophageal cancers are not inherited**
- **Genetic testing is cheap and widely available**
- **When genetic syndromes are identified in a family, it has a large positive impact!**
- **If you are concerned your family may be at risk, talk with you doctor**

Thank you

- I am happy to answer questions or help facilitate referrals
- Call Genetics at (614) 293-6694 for appointments
- @DocStanich



Thank You



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