Upper Gastrointestinal Cancers and the Role of Genetic Testing

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KEYWORDS

• Germline pathogenic variants • Upper gastrointestinal cancer • Gastric cancer
• Pancreatic cancer • Esophageal cancer • Genetic testing

KEY POINTS

- There are currently well-defined criteria for germline genetic testing in the setting of gastric and pancreatic cancer whereas these criteria are in evolution for esophageal and esophagogastric junction tumors beyond a limited number of well-defined genetic syndromes.
- Identification of novel associations is likely with expansion of access to germline genetic testing and the use of multi-gene panel testing.
- Germline variants in the homologous recombination deficiency (HRD) genes (*BRCA1/2, ATM, PALB2*) are increasingly being identified across a broad spectrum of tumor types beyond breast and ovarian cancer with potential therapeutic implications.
- Somatic-germline integration will be critical to determine relative causality of a particular germline pathogenic variant (gPV) to upper gastrointestinal carcinogenesis.

UPPER GASTROINTESTINAL CANCERS AND THE ROLE OF GENETIC TESTING

Evaluating the contribution of germline pathogenic variants (gPV) to the risk of any cancer is critical both for the appropriate estimation of lifetime cancer risks and potential preventative interventions but also increasingly due to potential therapeutic actionability.[1] Herein the authors will address the historical model of genetic testing and reflect on the limitations of this model,[2] define the most common high-risk genetic predisposition syndromes implicated in upper gastrointestinal carcinogenesis, and describe how germline genetic testing should be considered integral to the delivery of high-quality oncological care to both patients and their at-risk relatives.

The classic models of genetic testing for cancer are historically predicated on 3 basic factors: patient age at diagnosis with early-onset cancer conventionally being

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defined as cancer between 18 to 49 years, rarity of tumor type, and/or family cancer history. The aim of this approach is to identify those with the highest pre-test probability of having a gPV, while reducing the likelihood of obtaining uncertain results with limited clinical utility (eg, Variant of Uncertain Significance, VUS). This approach is centered on assessment as to whether a patient meets the "clinical criteria" for genetic testing. These criteria may be established by national guidelines specific to a particular cancer type, such as the National Comprehensive Cancer Network(NCCN) for Gastric Cancer,[3] or syndrome-specific criteria, such as the Amsterdam Criteria and Bethesda Guidelines[4,5] for assessment of and tumor screening for Lynch Syndrome (LS). While these criteria typically capture those at *highest* risk for having a gPV, over the last several years, an increasing amount of data has demonstrated that a significant portion of patients with gPVs in high penetrance cancer risk genes, such as the mismatch repair (MMR) genes diagnostic of LS, are missed through such stringent criteria. In a large cohort of patients with microsatellite instability (MSI) tumors, of those patients with LS presenting with cancers other than the canonical cancers (colorectal or endometrial cancers), only half met clinical testing criteria based on personal and/or family cancer history,[6] highlighting that relying on this "classic"testing model misses nearly half of LS diagnoses. Importantly, this is not unique to LS, as multiple studies have demonstrated a significant incremental pick-up rate for gPV in cancer susceptibility genes when classic testing criteria are relaxed.[7–9]

Gastric Cancer

Approximately 1% to 3% of gastric cancers are associated with gPVs[10] and genetically driven tumors are more common amongst patients with early onset disease. The most common syndrome is Hereditary Diffuse Gastric Cancer, associated with mutations in the *CDH1* [11–13] and more recently implicated *CTNNA1*[14] genes. Histologically this type of gastric cancer is characterized by multifocal diffuse spread with signet rings in the gastric mucosa. It is also associated with invasive lobular breast cancer when it arises in the context of a *gCDH1* mutation.

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (HDGC) accounts for approximately 1% of diffuse gastric cancer[15] and in 46% to 48% of these patients an e cadherin (*CDH1*) germline mutation is detectable.[15,16] *CDH1* is a tumor suppressor gene that encodes the for E-cadherin protein, an integral component of the adherens junctional complex in epithelial cells. This complex is implicated in cell-cell adhesion, invasion suppression, and signal transduction.[17] The description of a clear molecular basis for hereditary diffuse gastric cancer was first reported in 3 Maori kindred[13] with early onset diffuse type gastric cancer in the presence of germline inactivating e-cadherin/*CDH1* mutations. This was subsequently corroborated by a study of British and Irish familial gastric cancer kindreds[18] and in 3 European gastric cancer kindreds.[19] By 1999, 9 different germline *CDH1* mutations had been identified in European familial gastric cancer kindreds[18–20] and 14 had been described overall. A total of 80% of these carriers generate premature termination codons which ultimately result in impaired transcript loss and subsequent early onset gastric cancer.[21] These e-cadherin mutations in HDGC can occur throughout the *CDH1* gene[22] whereas in sporadic diffuse gastric cancer the mutations are observed in exons 7 to 9 of the gene.[23] In sporadic gastric cancer, truncating mutations are uncommon and sequence changes usually result in either missense mutations or exon skipping.[24] A further 13 novel mutations in *CDH1* were described in 2004[15] and a further 6 in 2007.[25]

The cumulative risk of developing gastric cancer in a patient with gPV in *CDH1* is approximately 37% to 64% in men and 24% to 47% in women.[18,26] The risk of breast cancer is approximately 39% to 55%[11,12,26,27] and the estimated combined risk of breast and gastric cancer by 75 is 78%.[12]

In 2010, recommendations for *CDH1* testing by the International Gastric Cancer Consortium[28] identified 4 criteria for *CDH1* testing: (I) Two family members with gastric carcinoma, 1 of which is confirmed diffuse gastric cancer; (II) 3 family members with gastric carcinoma in first-degree or second-degree relatives including 1 with diffuse gastric cancer; (III) One member with diffuse gastric cancer before the age of 40; (IV) Personal or family history of diffuse gastric cancer and lobular breast cancer including 1 diagnosed before 50. This was further refined in 2015[29] to recommend testing if (I) 2 gastric cancer cases in family members regardless of age, at least 1 confirmed to be diffuse gastric cancer, (II) One case of Diffuse Gastric Cancer <40, or (III) Personal or family history of Diffuse gastric cancer or Lobular breast cancer, 1 diagnosed <50. Patients and families in whom testing can be considered include those with bilateral lobular breast cancer or family history of 2 or more cases of lobular breast cancer at least 1 <50, a personal or family history of cleft palate in a patient with diffuse gastric cancer, or in situ signet ring cells and/or pagetoid spread of signet ring cells.

A confirmed gPV in *CDH1* should prompt prophylactic gastrectomy with large series demonstrating a high rate of signet ring cancers found in patients undergoing prophylactic risk-reducing surgeries.[30] Recent data, based on individuals with *CDH1* gPVs who declined surgical intervention, provocatively suggested endoscopic screening (Cambridge protocol) in dedicated centers with appropriate expertise may be an alternative to prophylactic surgery.[31] However, at the present time, this is not considered international best practice.

CTNNA1

Approximately 40% of hereditary diffuse gastric cancer was noted in families negative for CDH1 gPVs.[12] Beyond *CDH1* gPVs, hereditary diffuse gastric cancer can also be seen in the setting of truncating mutations in the *CTNNA1* (α catenin) gene inferring a genocopy of *CDH1*[12,32] although this represents a minority of diffuse gastric cancer families.[11] *CTNNA1* encodes for α catenin which partners with the e-cadherin protein in the adherens junctional complex. *CTNNA1* has only recently been classified as an HDGC predisposing gene due to the identification of loss of function variants in families fitting clinical criteria for hereditary diffuse gastric cancer.[31] Current guidelines now recommend similar surveillance (Cambridge protocol) for patients with confirmed truncating mutation in *CTNNA1* and prophylactic gastrectomy can be considered regardless of endoscopy findings. The clinical spectrum and age range of *CTNNA1* gPV carriers is less clearly characterized than CDH1 gPV carriers. Early onset diffuse gastric cancer is a frequently associated phenotype[14] ; however, pathogenic *CTNNA1* variants are not associated with lobular breast cancer.

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

Additionally, an autosomal dominant syndrome has been identified characterized by gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) without duodenal or colonic involvement in most individuals reported.[33,34] GAPPS arises in the context of *APC* promoter 1B mutations (c.-191T > C, c.-192A > G, and c.-195A > C) which reduce the binding activity of the transcription factor Yin Yang 1 (YY1) and transcriptional activity of the promoter.[35] The key clinical features of GAPPS are proximal gastric polyposis with hyperplastic and adenomatous polyps with antral

sparing; the malignant transformation potential of these polyps is also noted to be higher than in familial adenomatous polyposis (FAP). GAPPS is typically associated with intestinal type adenocarcinoma. In one of the most comprehensive overviews of 3 families[33] with this syndrome, the gastric phenotype was apparent from the age of 10 and the first gastric cancer occurred at age 38. It is not yet clear whether prophylactic gastrectomy should be considered in patients with GAPPS.

Lynch Syndrome

Lynch syndrome, caused by gPVs *in MLH1, MSH2, MSH6, PMS2*, and terminal deletions in *EPCAM*[36] is one of the most common cancer predisposition syndromes with a prevalence of approximately 1 in 279 people. It is characterized by a high proportion of tumors with MSI or deficient MMR on immunohistochemistry with protein loss reflective of the underlying germline variant. Furthermore, MSI-associated Lynch syndrome cancers should prompt reflexive germline genetic testing. A 2019 publication reported that among over 15,000 patients representing a pan-cancer cohort of MSI tumors (>50 cancer types), LS was identified in approximately 16% of the cases.[37] Early onset gastric cancer (non-diffuse type) may occur in the setting of Lynch syndrome. Cumulative incidences at 75 years (risks) for upper gastrointestinal (gastric, duodenal, bile duct, or pancreatic) cancers were 10%, 17%, and 13% in path_MLH1, path_MSH2, and path_MSH6 carriers, respectively, per the Prospective Lynch syndrome registry.[38] The identification of MSI gastric cancer may have important implication for treatment with immune checkpoint blockade in both the locally advanced and the metastatic disease settings,[39,40] as well as the need for on-going high-risk surveillance even in immunotherapy-treated Lynch syndrome patients.[41]

Li Fraumeni

Li Fraumeni is an autosomal dominant syndrome caused by pathogenic variants in *TP53.* LFS confers an 80% to 90% lifetime risk of cancer with up to 21% of cancers occurring before age 15[42] Classical Li Fraumeni-associated cancers include sarcoma, brain tumors, leukemia, breast cancer, and adrenocortical tumors; however, increasingly early onset gastric cancer has been recognized as a component of the syndrome[43] and endoscopic surveillance is considered an important component of comprehensive Li Fraumeni surveillance.[44]

Familial Adenomatous Polyposis Syndrome

Familial adenomatous polyposis (FAP) is caused by gPVs in *APC*.[36,45,46] Whilst the risk of colorectal cancer is very clearly defined and underpins the recommendation for prophylactic colectomy when *gAPC* is confirmed,[47] the risk of gastric cancer appears more modest[48] particularly amongst Western carriers of *gAPC* variants.

Peutz Jeghers

Peutz–Jeghers is an autosomal dominant condition distinguished by hamartomatous polyps in the gastrointestinal tract and pigmented mucocutaneous lesions. It is by caused by gPVs in *STK11*[49,50] and confers an increased risk of gastrointestinal, pancreatic, lung, breast, uterine, and testicular cancers.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome is caused by gPVs in *SMAD4* or *BMPR1A*.[51,52] It is also an autosomal dominant syndrome characterized by distinct polyps throughout the gastrointestinal tract both upper and lower. Gastric cancer risk appears to be greatest with gPV in *SMAD4*[53] with a rare but important phenotypic variant presenting with massive gastric polyposis and often very early onset gastric cancer.[54]

Importantly, many of the aforementioned syndromes have classic, well-described phenotypic presentations, allowing for better estimations of pre-test probability of a true-positive result in such cases.

Homologous Recombination DNA Repair Pathway

Mutations in the homologous recombination DNA (HRD) pathway are thought to account for a significant proportion of families with diffuse gastric cancer in the absence of *CDH1* or *CTNNA1* gPVs. Fewings and colleagues[55] performed whole exome sequencing in 22 families who had previously tested negative for *CDH1*. *PALB2* loss of function variants were significantly more common than in the general population. However, *PALB2* germline variants have also been identified amongst patients[56] with non-diffuse histology suggesting potential association with heterogenous histologic subtypes.[57]

Deleterious mutations in *ATM* have been found at a significantly higher frequency amongst patients with gastric cancer from diverse ethnic backgrounds [58]; this is further corroborated by genome-wide association studies.[58,59] Gastric cancers arising in patients with *gATM* may potentially be susceptible to targeted approaches.[60]

The association with *BRCA1/2* with gastric cancer risk has been considered an issue of debate for some time. In a large cohort of over 5000 *BRCA* families, the relative risk of gastric cancer was increased in both *BRCA1* and *BRCA2* carriers, 2.17 (95% CI 1.25–3.77)-fold and 3.69 (95% CI 2.4–5.67)-fold, respectively.[61] This association appears to be stronger with *BRCA2* than with *BRCA1*.[62–65] Additionally, risk appears to potentially be modified by the presence of *Helicobacter pylori*.[66] At the present time, these data are not robust enough to recommend routine surveillance gastroscopy in all carriers of gPVs in *BRCA* but it would not be unreasonable in the setting of both gPVs and a family history of gastric cancer.[67] Arguably these current data would suggest that screening patients with gPV in *BRCA* at baseline for the presence of *Helicobacter pylori* should be considered.

Similar to data from other cancer types with increasing access to multigene panel testing (MGPT), gPVs potentially implicated in gastric cancer will be identified even in patients without a family history.[68]

Esophageal Cancer

Per the most recent NCCN guidelines (Version 3, 2023), specific referral guidelines for esophageal and esophagogastric junction (EGJ) cancers from the perspective of genetic risk assessment are not yet possible at this time. In contrast to gastric cancer, there are a relatively limited number of defined genetic syndromes recognized to be associated with an increased risk of esophageal cancer.

Esophageal Cancer, Tylosis with Non-epidermolytic Palmoplantar Keratoderma (PPK), and Howel–Evans Syndrome

Tylosis with esophageal cancer (TEC) is a very rare condition with an autosomal dominant pattern of inheritance and is caused by germline mutations in the *RHBDF2* gene. Individuals with germline RHBDF2 mutations have an increased risk for squamous cell carcinoma (SCC) of the middle and distal esophagus. Palmoplantar keratoderma (PPK) is divided into diffuse, punctate, or focal patterns of skin thickening on palms and soles. The risk of esophageal carcinoma has been calculated to be 95% by 65 years of age in 1 large family but the frequency of the disorder in the general population is unknown.[69]

Bloom Syndrome

Bloom syndrome (BS) is a rare autosomal recessive disorder characterized by mutations of the *BLM* gene at 15q26.1[70] and is associated with strikingly elevated sister

chromatid exchange rates in all cells. Patients with BS are affected by acute myeloid leukemia, acute lymphoblastic leukemia, or lymphoid neoplasms at an early age and one-third of patients with BS have multiple independent malignancies.[71] Patients with BS appear to have 150 to 300 times greater risk of cancer development than those without this disorder[72] including SCC of the esophagus after 20 years of age.

Fanconi Anemias

The genes involved in Fanconi anemia (FA) include FA complementation groups A–E, with FA-A (FANCA) located at 16q24.3; FA-B (FANCB), unknown; FA-C (FANCC) at 9q22.3; FA-D (FANCD) at 3p26–p22; and FA-E (FANCE), unknown. Patients with germline variants *FANCA* and *FANCC* are affected by pancytopenia and chromosome breakage and hematologic abnormalities, including anemia, bleeding, and easy bruising. An increased frequency of SCC of the esophagus has been described in these patients.[73]

Familial Barrett esophagus

Familial Barrett esophagus[74] (FBE) includes adenocarcinoma of the esophagus and EGJ. Inheritance appears to be autosomal dominant and several potential candidate genes have been identified but causality has not been clearly validated.

Two more contemporary studies[75,76] have raised the question of the contribution of gPVs in ATM to esophageal adenocarcinoma risk, a potential association that will require further evaluation.

Gastroesophageal Junction Cancer

Gastroesophageal Junction (GEJ) cancers are unique in that these tumors are thought to reflect a mix of true GEJ tumors as well as proximal gastric and distal esophageal cancers, which may be clinically indistinguishable. Indeed, The Tumor Genome Atlas analysis of esophageal cancers found a gradual transition of molecular subtypes from the distal esophagus to the GEJ and then to the proximal stomach.[77] In line with this observation, in studies utilizing MGPT, the prevalence of gPV in GEJ cancers was higher than in esophageal but lower than in gastric cancers.[78] Given the difficulty in accurately classifying the origin of any GEJ cancer, following guidelines for gastric cancer genetic testing recommendation are probably a reasonable recommendation.

Pancreatic Cancer

The contribution of pPVs, particularly those in the HRD pathway, is increasingly being recognized in pancreatic cancer. In a pan cancer analysis of approximately 12,000 patients, 19.6% of the patients with pancreatic ductal adenocarcinoma (PDAC) were found to harbor pathogenic germline variants.[1] The likelihood of a positive genetic test appears higher amongst patients with early onset disease; in a cohort of 450 early onset pancreatic cancer patients diagnosed between 2008 to 2018 at a large academic institution,[79] approximately 32% were found to harbor at least 1 gPV, with 27.5% of gPVs identified in high and moderate penetrance genes.[79] This is corroborated by a large study from another US tertiary center which demonstrated that patients with early onset (EO) pancreatic cancer had a significantly higher odds of testing positive than older patients for germline mutations (OR 1.93; 95% CI 1.03–3.7), although the definition of early onset pancreatic cancer for the purposes of this study was defined as aged <60.[80] Of particular concern is that, the incidence in patients <50 years of age appears to be rising.[81–83] Understanding the contribution of gPV to this rising incidence is important particularly as the efficacy of pancreatic

cancer screening amongst carriers of implicated gPVs is increasingly being corroborated.[84]

The HRD genes most commonly implicated in pancreatic cancer are *BRCA2* (5%–10%),[85,86] PALB2 (2%–3%),[87,88] ATM(3%–4%),[89,90] and BRCA1 (1%).[91] The initial studies from the Breast Cancer Linkage Consortium valuating contribution of BRCA1/2 to breast cancer risk[92,93] also suggested an association between *BRCA1* and *BRCA2* mutations and prostate and pancreatic adenocarcinomas as well (particularly for *BRCA2*), and subsequent research has further confirmed these associations. The potential actionability of these germline findings was underscored by the efficacy of polyp ADP ribose polymerase inhibitor (PARPi) in the POLO study of maintenance Olaparib among g*BRCA*-carriers with metastatic pancreatic cancer.[94]

Table 1
High and moderate penetrance gPVs in upper gastrointestinal cancer and therapeutic actionability

Pathogenic Germline Variant	Cancer Subtype	Gene Penetrance	Targetable	Therapeutic Agent
ATM	Gastric Esophageal Pancreas Biliary	Moderate	No	-
APC	Gastric	High	No	-
BRCA1/2	Pancreas Gastric[a] Biliary	High	Yes	PARPi
PALB2	Gastric Pancreas Biliary	Moderate	Yes	PARPi
CDH1	Gastric	High	No	-
CDKN2A	Pancreas	High	Not at present	Negative trial of CDK4/6i
CTNNA1	Gastric	High	No	-
MLH1	Gastric Pancreas	High	Yes[a]	ICB
MSH2	Gastric Pancreas	High	Yes[a]	ICB
MSH6	Gastric Pancreas	High	Yes[a]	ICB
PMS2	Gastric Biliary	High	Yes[a]	ICB
PRSS1	Pancreas	High or low dependent on variant	No	-
STK11	Gastric Pancreas	High	No	-
SMAD4	Gastric	High	No	-
BMPR1A	Gastric	High	No	-
TP53	Gastric Esophageal	High	No	-

Abbreviations: CDK4/6i, cyclin-dependent kinase inhibitor; ICB, immune checkpoint blockade; PARPI, polyp ADP ribose polymerase inhibitor.

[a] Actionable in the setting of tumors with Microsatellite Instability (MSI).

The association of *ATM* with pancreatic cancer was identified through genome-wide sequencing in 2012[89] and has been further corroborated in a number of studies.[90] More recent data characterizing somatic and germline *ATM* variants arising in association with pancreatic ductal adenocarcinoma demonstrated an improved OS in this cohort[95,96]; interestingly *ATM* was not found to confer an HRD signature suggesting limited benefit from strategies exploiting this pathway.

Germline variants in *CDKN2A* have been reported to confer a 12.3-fold increased risk of pancreatic cancer[91,96,97] while additionally, although rare, *gSTK11* mutations have been reported to confer a 130-fold increased risk.[49] Pancreatic cancer has also been described in association with the LS-associated genes; this risk of pancreatic cancer may vary by germline MMR variant[98] and the risk is approximately 8.6-fold greater than the general population.[99] Recognition of LS-associated pancreas cancer is potentially actionable given recent data regarding the utility of immune checkpoint blockade in this cohort in the setting of MSI disease.[40,100]

NCCN guidelines[101] now recommend germline genetic testing for all patients diagnosed with pancreatic cancer with results guiding need for cascade testing within families and potentially enrollment into pancreatic surveillance protocols for unaffected familial carriers of gPVs. Notably, despite extensive gene discovery research efforts, a large proportion of familial pancreatic cancer, defined as a kindred with at least a pair of first-degree relatives with pancreas cancer,[102] remains genetically unexplained.[96] As in patients with gPV in pancreas-associated cancer susceptibility genes and a family history of the disease, pancreatic surveillance should also be considered in the context of individualized decision-making in first-degree relatives of individuals with familial pancreatic cancer.[103]

Biliary Tract Cancer

The data for the contribution of gPVs to biliary tract cancers inclusive of cholangiocarcinoma and gallbladder cancer are much more limited. One study in a predominantly Caucasian population reported gPVs in 16% of the patients[104] with 9.9% of these in high and moderate penetrance cancer predisposition genes. This is comparable to a reported gPV rate of 11% in a Japanese cohort of patients with biliary cancer[105] although the variants identified differed. These rates are comparable to other solid tumors, however, and support integration of germline genetic testing in the management of these patients.

SUMMARY

With increasing availability of commercial multigene panel testing (MGPT) and expansion of the cancer types in which MGPT is recommended, particularly in patients with early onset cancer, we will undoubtedly detect more gPVs which are of clinical relevance for the cancer-affected patient as well as at-risk relatives. While criteria for germline genetic testing are more clearly defined for gastric cancer[3] and pancreatic cancer,[101,106] guidelines in relation to the role of genetic testing for more novel genes[75] in the setting of esophageal cancer beyond a limited number of cancer predisposition syndromes, and in biliary cancer, is in evolution.[105,107] Increased access to commercial panels and more widespread integration of genetic testing into cancer care will enhance appreciation of novel associations and our understanding of the contribution of these variants to gastrointestinal carcinogenesis will become more clearly defined (**Table 1**).

It is important to caution that the relative contribution of a gPV detected on MGPT to causation of the index cancer particularly in the setting of genes not classically

associated with that cancer subtype is challenging to deduce. Integration of germline and somatic analysis is critical to elucidate the role of germline variants in upper gastrointestinal carcinogenesis by evaluating bi-allelic loss, which, when assessed, seems to be consistently higher among patients with early onset cancer than in average onset cancer.[108,109] This suggests that these gPVs are driving cancer development at least in a proportion of these cancers. Determination of causality is imperative in order to identify novel treatment approaches exploiting underlying germline drivers implicated in carcinogenesis. Potential actionability of these underlying gPvs as exemplified by the utility of PARPi and immunotherapy is particularly pertinent.

While the prevalence of gPVs is consistently higher amongst patients with early onset cancers, decisions regarding germline genetic testing should not be restricted by age alone or by an arbitrary designation of young onset. In a review of 25,035 patients with cancer,[2] an age cutoff of 50 for early onset cancer was >1 standard deviation below the mean age at diagnosis in 20 cancer types resulting in 2226 patients who would not have been classified as having early onset cancer, inclusive of 394 patients who tested positive for a germline LP/P, representing 26.1% of all germline early onset cancer positives. These findings are particularly relevant as the therapeutic implication of gPVs expands.[110,111]

CLINICS CARE POINTS: PEARLS AND PITFALLS

- Comprehensive management of upper gastrointestinal cancers should incorporate germline genetic testing.
- Stringent application of clinical criteria for genetic testing in any cancer type, including gastric, esophageal, GEJ, pancreatic, or biliary cancer, may miss a significant proportion of patients with underlying germline pathogenic variants (gPVs).
- Critically, germline genetic testing should not be restricted exclusively by definition of early onset cancer as cancer arising <50 years of age, and family history should always be integrated into clinical decision-making
- Identification of germline pathogenic variants may increasingly have implications for systemic therapy decisions

DISCLOSURE

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