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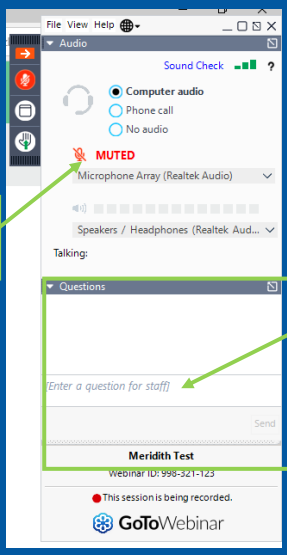

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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Week 40 – Thursday, October 6, 2022
Refractory, Recurrent Ulcer Disease and Persistent Gastritis: New Management Strategies
Faculty: Nimish Vakil, MD, FACG
Moderator: Nalini Guda, MD, FACG
Thursday, October 6th at Noon Eastern and NEW! **8pm Eastern!**

Week 41 – Thursday, October 13, 2022
C. Diff Infection Treatment: What Is New?
Faculty: Monika Fischer, MD, MS, FACG
Thursday, October 13th at Noon Eastern and NEW! **8pm Eastern!**

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2022 CGA-IGC Annual Meeting
The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer
#CGAIGC22
Nashville
November 11-13, 2022
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Disclosures

Gregory E. Idos, MD

No relevant financial relationships with ineligible companies

Veroushka Ballester, MD

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Diagnosis and Management of Cancer Risk in the Gastrointestinal Hamartomatous Polyposis Syndromes: Recommendations from the US Multi-Society Task Force on Colorectal Cancer

GREGORY IDOS MD, MS

Associate Professor of Medicine
Division of Gastroenterology
Center for Precision Medicine
City of Hope National Medical Center

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Hamartomatous Polyposis Syndromes

- The gastrointestinal hamartomatous polyposis syndromes are rare, autosomal dominant disorders
  - Peutz-Jeghers syndrome (PJS)
  - Juvenile polyposis syndrome (JPS)
  - *PTEN* hamartoma tumor syndrome (PHTS) (including Cowden's syndrome)
  - Hereditary mixed polyposis syndrome (HMPS)
- Associated with an increased risk of benign and malignant intestinal and extra-intestinal tumors.

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CANCER FAMILY HISTORY ASSESSMENT AND REFERRAL FOR GENETIC TESTING IN GI PRACTICE

- The collection and assessment of family cancer history is a valuable tool for cancer interception and prevention and can be critical in the identification of genetic susceptibility.
- An accurate family history is one that collects the following information:
  - Type of cancer(s),
  - Age at diagnosis of each primary cancer
  - Lineage (maternal or paternal),
  - Ancestry(people of some ethnicities, such as those with Ashkenazi Jewish ancestry, are at greater risk for certain cancers),
  - Results of any previous cancer-related genetic testing.

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Which individuals with hamartomatous polyps should be referred for genetic evaluation?

- We recommend patients with any of the following undergo a genetic evaluation
  - Two or more lifetime hamartomatous polyps
  - A family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives.
  - Genetic testing (if indicated) should be performed using a multigene panel test. (Strong recommendation, low quality evidence)

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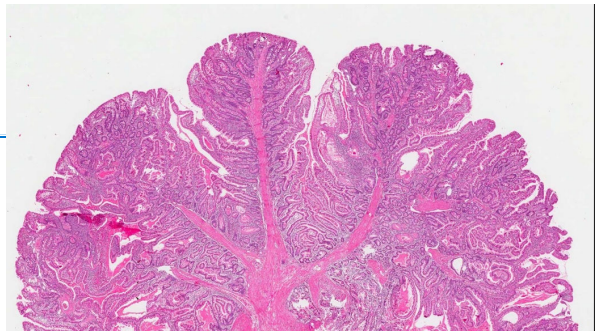
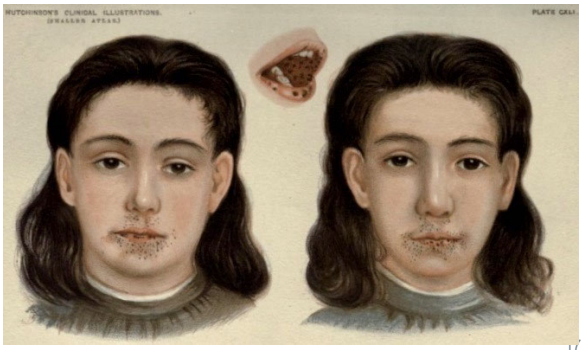
Peutz-Jeghers syndrome

- First hamartomatous polyposis syndrome described, by Peutz in Holland in 1921 and by Jeghers, McKusick and Katz in the US in 1949.
- Characteristic features:
  - Mucocutaneous freckling around the mouth
  - Multiple cerebriform appearing polyps due to smooth muscle bands coursing through the polyp





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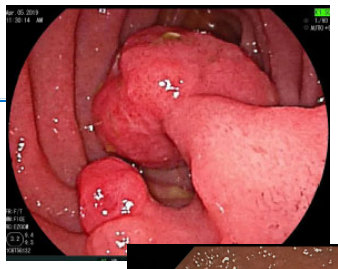
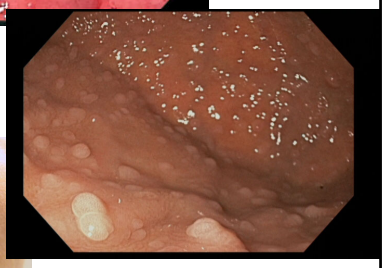
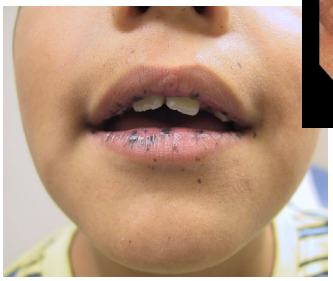
Peutz-Jeghers Syndrome (PJS)

- Pathogenic germline variants in the *STK11* gene
- Autosomal Dominant
- Risk of intussusception is 50%-68% by age 18
- Clinical management
  - Children-Focused on preventing complications of small bowel polyps
  - Adults-Focus primarily on management of cancer risk.







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Who should undergo a genetic evaluation for Peutz-Jeghers syndrome?

We recommend genetic evaluation for any individual with the following:

- Two or more histologically confirmed Peutz-Jeghers polyps,
- Any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first degree relative
- Characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome
- Any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. (Strong recommendation, low quality evidence)

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Which organs should undergo surveillance when caring for a Peutz-Jeghers syndrome patient?

- Patients with Peutz-Jeghers syndrome are at increased risk for cancer in multiple organs including cancer of the breast, small bowel, colon, stomach, pancreas, ovaries, testes, and lungs.
- Given this risk, we recommend a multi-disciplinary approach to cancer surveillance in these organs (Strong recommendation, low quality evidence)

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Site	General Population Risk[1]	Syndrome Risk	Average Age of Diagnosis (years)
Peutz-Jeghers syndrome			
Colorectal	4.3%	39%	42-46
Stomach	<1%	29%	30-40
Small Bowel	<1%	13%	37-42
Breast	12.9%	32%-54%	37-59
Ovarian (mostly SCTAT)	1.2%	21%	28
Cervix (adenoma malignum)	<1%	10%-23%	34-40
Uterus	3.1%	9%	43
Pancreas	1.7%	11%-36%	41-52
Testicular (Sertoli cell tumor)	<1%	9%	6-9
Lung	6.3%	7%-17%	47

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Surveillance of patients with PJS

- How and when should small bowel surveillance be performed in Peutz-Jeghers syndrome?
- What is the recommended approach to endoscopic surveillance of the colon, stomach and duodenum in Peutz-Jeghers syndrome?
- What size polyps found on small bowel imaging *in Peutz-Jeghers syndrome* should be removed?
- What is the recommended pancreatic cancer surveillance in Peutz-Jeghers syndrome?

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Cancer Surveillance for PJS

Site	Population Risk	Lifetime Risk	Screening Procedure and Interval	Initiation Age (Y)
Colorectal	4.3%#	40%#	Colonoscopy every 2-3 years*#	8-10,18*
Gastric	<1%#	29%#	Upper endoscopy every 2-3 years*#	8-10,18*
Small Bowel	<1%#	13%#	Video Capsule Endoscopy every 2-3 years*	8,18*
Pancreas	1.7%#	11%-36% #	MRI/MRCP or EUS of pancreas annually#	35

* Colonoscopy, EGD and small bowel surveillance resumes at age 18 if normal between ages 8-10.

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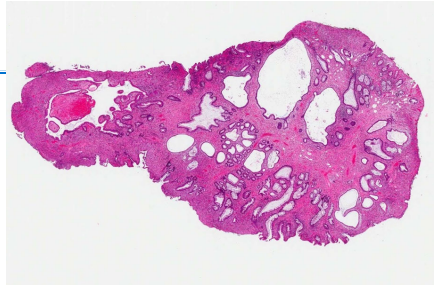
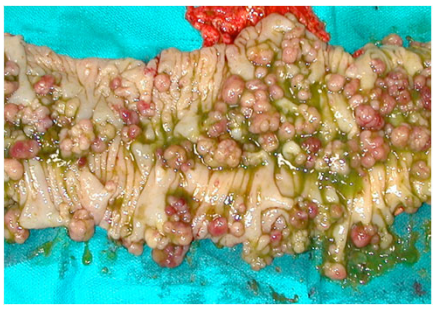
Juvenile Polyposis Syndrome (JPS)

- Autosomal-dominant inherited condition
- Incidence between 1 in 100,000 and 1 in 160,000
- Multiple juvenile polyps founds in the colon, stomach, and small intestine.
- Solitary juvenile polyps are not syndromic
- Pathogenic germline variants in the *SMAD4* or *BMPR1A* gene





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Who should undergo a genetic evaluation for Juvenile polyposis syndrome?

We recommend genetic evaluation for any individual with

- Five or more juvenile polyps of the colon or rectum
- Two or more juvenile polyps in other parts of the gastrointestinal tract
- Any number of juvenile polyps and one or more FDRs with Juvenile polyposis syndrome. (Strong recommendation, low quality evidence)

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Which organs should undergo surveillance when caring for a Juvenile polyposis syndrome patient?

- Juvenile polyposis syndrome patients are at increased risk for cancer in multiple organs including cancer of the colon and stomach.
- Given this risk, we recommend patients with Juvenile polyposis syndrome undergo surveillance of the colon and stomach. (Strong recommendation, low quality evidence)

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Colorectal Cancer surveillance for JPS

Site	Population Risk	Lifetime Risk	Screening Procedure and Interval	Initiation Age (Y)
Colorectal	4.3%#	39% #	Colonoscopy every 1-3 years#	12-15 years*
Stomach	<1%#	5-21%#	Upper Endoscopy every 1-3 years#	12-15 years*

*Colonoscopy can begin earlier that age 12 if there are symptoms, especially rectal bleeding

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Which patients with Juvenile polyposis syndrome should undergo screening for hereditary hemorrhagic telangiectasia (HHT)?

- We suggest patients with SMAD4 pathogenic variants be clinically evaluated for HHT at the time of the diagnosis, including screening for and appropriate management of cerebral and pulmonary AVMs. (Weak recommendation, low quality evidence)

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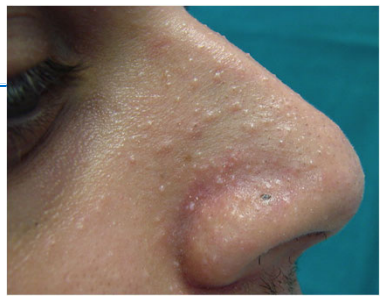
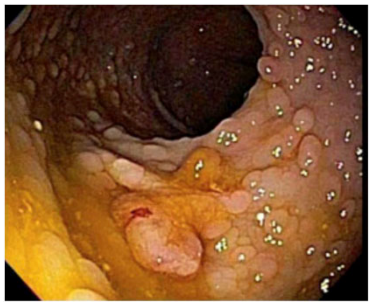
Cowden syndrome



- Part of a spectrum of PTEN-hamartoma syndrome
  - Bannayan-Riley-Ruvalcaba syndrome
  - Proteus syndrome
- Pathogenic germline variants in the *PTEN* gene
- Gastrointestinal polyps are frequently found- hyperplastic polyps, inflammatory polyps, ganglioneuromas, adenomas



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Cowden Syndrome Clinical Criteria

REVISED CLINICAL DIAGNOSTIC CRITERIA FOR PTEN HAMARTOMA TUMOR SYNDROME[a]

MAJOR CRITERIA:
- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- GI hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97th percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - Multiple trichilemmomas (≥3, at least one biopsy proven)
  - Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - Mucocutaneous neuromas (≥3)
  - Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

MINOR CRITERIA:
- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthoses (≥3)
- Lipomas (≥3)
- Intellectual disability (ie, IQ ≤75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)
- Vascular anomalies/malformations (including multiple intracranial developmental venous anomalies)

Operational diagnosis in an individual (either of the following):
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or
2. Two major and three minor criteria.

Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* pathogenic/likely pathogenic variant:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

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Which gastrointestinal findings should prompt a genetic evaluation for *PTEN* hamartoma tumor syndrome?

- We recommend individuals with multiple gastrointestinal hamartomas or ganglioneuromas undergo genetic evaluation for Cowden's syndrome and related conditions. (Strong recommendation, low quality evidence)

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Which organs should undergo surveillance for cancer when caring for a *PTEN* hamartoma tumor syndrome patient?

- PTEN hamartoma tumor syndrome patients are at increased risk for cancer in multiple organs including cancer of the breast, thyroid, kidney, uterus, colon, and skin.
- Given this risk, we recommend a multi-disciplinary approach to cancer surveillance in these organs (Strong recommendation, low quality evidence)

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Site	General Population Risk	Syndrome Risk	Average Age of Diagnosis (years)
Cowden syndrome			
Breast	12.9%	25-85%	38-46
Thyroid	1.3%	3-38%	31-38
Uterus	3.1%	5-28%	25
Kidney (renal cell)	1.7%	15-34%	40
Colon	4.3%	9%-18%	35
Melanoma	2.3%	6%	3*

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What is the recommended colonoscopic surveillance in individuals identified with *PTEN* hamartoma tumor syndrome?

- We suggest colonoscopy surveillance to begin at age 35 years, repeated at intervals no greater than 5-years, depending on polyp burden. (Weak recommendation, low quality of evidence)

Site	Population Risk	Lifetime Risk	Screening Procedure and Interval	Initiation Age (Y)
Colorectal	4.3%#	9-18% #	Colonoscopy every 5 years#	35 years

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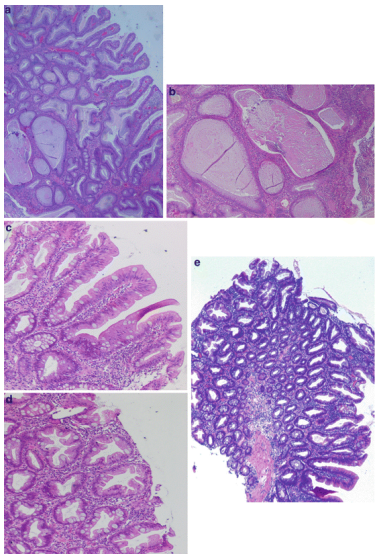
Hereditary Mixed Polyposis Syndrome (HMPS)

- HMPS is a rare autosomal dominant disease reported in only a few families.
- Attenuated colonic polyposis.
  - Hyperplastic
  - Particular polyp with an admixture of variable histologies including: adenomatous, hyperplastic, juvenile and mixed polyps
- Large duplications of the promoter region or entire *GREM1* gene



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Knowledge Gaps

- Discover the germline variants in families with clinically recognizable syndromes who do not have germline mutations in the genes known to be associated with these syndromes.
- Understand the effects of haplo-insufficiency of *STK11* in PJS and the *SMAD4* in JPS on the development of polyposis.
- Identify safe and effective pharmacological interventions for the inhibition of polyp formation children and adults with the hamartomatous polyposis syndromes.
- Determine whether pharmacological intervention can mitigate cancer risk in PJS and JPS in adults (independent of the polyposis risk).
- Design and implement studies to determine the best imaging modalities and surveillance intervals in adults with a hamartomatous polyposis syndrome.
- Perform outcomes studies evaluating the transition of care in pediatric polyposis patients entering adult life, including outcomes such as compliance with surveillance.
- Determine the lifetime cancer risks in patients with a pathogenic variant, but without clinical manifestations (those identified incidentally on multi-gene panel testing).

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Summary

- The identification of individuals with a hereditary gastrointestinal cancer syndrome requires a thorough evaluation of the patient's personal and family history of cancer.
- We recommend genetic evaluation for those with 1)Two or more lifetime hamartomatous polyps 2) A family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. 3)Genetic testing (if indicated) should be performed using a multigene panel test.
- GI Surveillance in patients with a Hamartomatous Polyposis Syndrome may be initiated in affected children focusing primarily on the risk of intussusception, obstruction or GI bleeding
- As affected children grow older and transition into adulthood, the focus shifts to managing the cancer risk.

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Questions and Answers

Gregory E. Idos, MD

Veroushka Ballester, MD

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