Diagnosis and Management of Hereditary Polyposis

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Disclosures

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• Consultant: SLA Pharma, Janssen Pharma

• Member: US Multi-Society Task Force on Colorectal Cancer, National Comprehensive Cancer Network Guideline on Genetic/Familial High-Risk Assessment: Colorectal
Learning objectives

- *Categorize* hereditary polyposis syndromes by colon polyp histology
- *Recognize* diagnostic features of the most common hereditary adenomatous syndromes
- *Understand* recommended management strategies for individuals/families with hereditary adenomatous polyposis
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Features (all include CRC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td>APC</td>
<td>Colorectal/duodenal adenomas/Ca, gastric polyposis/Ca, thyroid cancer, osteomas, soft tissue tumors, adrenal adenomas, desmoids</td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td>MUTYH</td>
<td>Similar to FAP with attenuated features</td>
</tr>
<tr>
<td>NTHL1-associated polyposis</td>
<td>NTHL1</td>
<td>Colorectal/duodenal adenomas; breast/endometrial/urothelial cancer; meningioma</td>
</tr>
<tr>
<td>Polymerase proofreading associated polyposis</td>
<td>POLE, POLD1</td>
<td>Colorectal adenomas; endometrial/ovary/brain cancer</td>
</tr>
<tr>
<td>MSH3-associated polyposis</td>
<td>MSH3, MLH3</td>
<td>Colorectal/duodenal adenomas; gastric cancer; early-onset astrocytoma Colorectal adenomas; breast ca</td>
</tr>
<tr>
<td>MLH3-associated polyposis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AXIN2-Associated Polyposis</td>
<td>AXIN2</td>
<td>Oligodontia, ectodermal dysplasia, duodenal/CR adenomas, CRC/HCC/breast/lung/prostate ca</td>
</tr>
<tr>
<td>Constitutional Mismatch Repair Deficiency (CMMRD)</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Colorectal/duodenal adenomas/Ca, brain tumors, hematologic malignancies, café au lait spots</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11</td>
<td>Mucocutaneous pigmentation, GI hamartomas; rare GYN/testicular cancers breast/pancreatic/gastric/SB/uterine ca</td>
</tr>
<tr>
<td>PTEN Hamartoma Tumor Syndrome</td>
<td>PTEN</td>
<td>Intestinal hamartomas, glycogen acanthosis, skin lesions, macrocephaly, breast/thyroid/renal/endometrial ca</td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td>BMPR1A, SMAD4</td>
<td>Gastric/colorectal hamartomas, gastric cancer, SMAD4 –HHT overlap</td>
</tr>
</tbody>
</table>
Syndromic and Phenotypic Overlap

- Lynch Syndrome
  - Molecular or Clinical Dx
  - Clinical Dx
- FCC Type X
- HNPCC
- PTHS
  - Molecular or Clinical Dx
- PJS
  - Molecular or Clinical Dx
- JPS
  - Clinical or Molecular Dx
- HMPS
  - Molecular Dx
- MAP
- SPS
  - Clinical or Molecular Dx
- NTHL1
  - PPAP
  - AXIN2
  - MSH3
- FAP
  - Molecular Dx
- Clinical or Molecular Dx
- Molecular or Clinical Dx
- Clinical Dx
- Molecular Dx
Germline Polyposis Syndromes

- Familial Adenomatous Polyposis
- MUTYH-Associated Polyposis*
- Polymerase Proofreading Polyposis
- AXIN-2 Associated Polyposis
- MSH3 Associated Polyposis*
- MLH3 Associated Polyposis*
- NTHL1 Associated Polyposis*

Germline DNA Mismatch Repair Deficiency Syndromes

- Constitutional MMR Deficiency (CMMRD)*

Not Genetically Defined/Environmental

- Colonic Polyposis of Unknown Etiology
- Familial CRC Type X
- Serrated Polyposis Syndrome
- Therapy Associated Polyposis

* Autosomal recessive
Hereditary Polyposis Syndromes

- Hereditary adenomatous polyposis syndromes are cancer predisposition syndromes, CRC and other organs
- Entry points into your practice
  - At time of colonoscopy
  - Office visit
    - Personal or family cancer or polyp history
    - Referred for positive result on multi gene panel test
Recognizing Hereditary Polyposis and Colorectal Cancer Syndromes

**Personal History**
- Early onset intestinal and extra-intestinal tumors
- Pathology of tumors
- Number/size of polyps
- Extra-intestinal features

**Family Cancer History**
- Gather in 3 generations
- Occurrence and age of cancer or polyps
- Age and cause of death
- Presence of features within spectrum of hereditary polyposis
### Hereditary CRC Syndrome Screener

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

- **Do you have a **first-degree relative** (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?**
  - Colon or rectal cancer
  - Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain

- **Have you** had any of the following conditions diagnosed before age 50?
  - Colon or rectal cancer
  - Colon or rectal polyps

- **Do you have three or more relatives with a history of colon or rectal cancer?**
  (this includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins)

---

**Identified 77% of high-risk individuals and 95% of LS mutation carriers**

Prevalence of Germline Pathogenic Variants in *APC* and 2 common *MUTYH* genes

N= 8676
Full sequencing and large rearrangement of *APC*
Targeted sequencing of *MUTYH* (Y179C and G396D)

<table>
<thead>
<tr>
<th>Cumulative Adenoma Count</th>
<th>Mutation Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>5%</td>
</tr>
<tr>
<td>10-19</td>
<td>9%</td>
</tr>
<tr>
<td>20-99</td>
<td>17%</td>
</tr>
<tr>
<td>100-999</td>
<td>63%</td>
</tr>
<tr>
<td>≥1000</td>
<td>82%</td>
</tr>
</tbody>
</table>

In both cohorts, 33% patients with pathogenic variant did not meet genetic testing criteria for the gene(s) in which they had a mutation.
Prevalence of Germline Pathogenic Variants in CRC by Age

Age <35 years
- Lynch syndrome 23%
- Polyposis syndromes 9%
- Other variant 2%
- None 65%

Age <50 years
- Lynch syndrome 10%
- Polyposis syndromes 3%
- Other variant 5%
- None 80%

Age >50 years
- Lynch syndrome 3%
- Polyposis syndromes <1%
- Other variant 6%
- None 90%

<table>
<thead>
<tr>
<th>Lynch syndrome</th>
<th>Polyposis syndromes</th>
<th>Other pathogenic variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>APC</td>
<td>BRCA1</td>
</tr>
<tr>
<td>MSH2</td>
<td>MUTYH</td>
<td>BRCA2</td>
</tr>
<tr>
<td>MSH6</td>
<td>SMAD4</td>
<td>TP53</td>
</tr>
<tr>
<td>PMS2</td>
<td>BMPR1A</td>
<td>PALB2</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>CDKN2A</td>
</tr>
<tr>
<td></td>
<td>POLE</td>
<td>BRIP1</td>
</tr>
</tbody>
</table>

Stoffel, Gastroenterology. 2020; 158(2): 341–353
## Indications for Polyposis Genetic Testing

<table>
<thead>
<tr>
<th>Family History</th>
<th>Personal History</th>
<th>Consider Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known germline pathogenic variant</td>
<td>&gt; 20 cumulative adenomas</td>
<td>10-19 cumulative adenomas</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 hamartomas</td>
<td>Desmoid tumor</td>
</tr>
<tr>
<td>Meets clinical criteria for polyposis syndrome and no germline testing done in affected relatives</td>
<td>Multi-focal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)</td>
<td>Cribiform-morula variant of papillary thyroid cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral CHRPE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meets WHO Criteria for Serrated Polyposis Syndrome with some adenomas</td>
</tr>
</tbody>
</table>

Adapted from NCCN guidelines V1.2021 Genetic Familial High-Risk Assessment: Colorectal
Recommendations for Multi-Gene Panel Testing for Hereditary CRC

- CRC diagnosed < 50 yrs
- Multiple Lynch syndrome* cancers
- CRC and ≥ 1 FDR with CRC or endometrial cancer
- PREMM5 score ≥ 2.5% or MMRpro, or MMR predict score ≥ 5%
- MMR deficient CRC not due to MLH1 promoter methylation
- Patients meeting other genetic testing criteria
- ≥ 10 cumulative colorectal adenomas
- ≥ 3 cumulative GI hamartomatous polyps

*CRC, endometrial, urothelial, small bowel, gastric, pancreatic/biliary tract, sebaceous carcinoma, glioblastoma

Case 1. August 1 2020 Virtual Visit

- 43 yr old male: change in BMs, rectal bleeding
- January started saw palmetto for urinary symptoms and it helped resolve those symptoms but bowel habits started to change
  - Frequent, bloody, tenesmus, nausea, no weight loss or systemic features
  - Past Medical History: nephrolithiasis
  - Family History: no IBD, CRC or other cancers, brother 60 had “polyps”
- Height 6’2” weight 290
- Labs CBC, CMP, Sed rate, CRP, stool infectious panel: normal
- Colonoscopy: 6, 6-25 mm polyps and …..
Case 1.

• Pathology:
  1. Colon, ascending, transverse, and descending, polyps: Tubular and tubulovillous adenomas
  2. Colon, sigmoid, tumor, biopsy: Invasive adenocarcinoma, moderately differentiated

MMR Status Report - Immunohistochemistry staining for mismatch repair proteins: Normal
MLH1, PMS2, MSH2, and MSH6 proteins expressed in cancer nuclei. Mismatch repair (MMR) status: Proficient (microsatellite stable)

• Low Anterior Resection and colo-colic anastomosis
  • Adenocarcinoma invades pericolonic adipose tissue; surgical margins negative.
  • Perineural and lymphovascular space invasion noted, including extramural venous invasion.
  • Metastatic adenocarcinoma in two lymph nodes (2/28).
  • Approximately 4, 2-4 mm polyps noted in the specimen, Tubular adenomas, Hyperplastic polyps.
Differential Diagnosis and Next steps?

Recommendations for Multi Gene Panel Testing

- CRC diagnosed < 50 yrs
- Multiple Lynch syndrome* cancers
- CRC and > 1 FDR with CRC or endometrial cancer
- PREMM5 score ≥ 2.5% or MMRpro, or MMR predict score ≥ 5%
- MMR deficient CRC not due to MLH1 promoter methylation
- Patients meeting other genetic testing criteria
- > 10 cumulative colorectal adenomas
- ≥ 3 cumulative GI hamartomatous polyps
Case 1. Next Steps

• Genetic counseling, multi gene panel testing

Two Pathogenic variants identified in MUTYH. MUTYH is associated with autosomal recessive MUTYH-associated polyposis.

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT</th>
<th>ZYGOITY</th>
<th>VARIANT CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUTYH</td>
<td>c.1187G&gt;A (p.Gly396Asp)</td>
<td>heterozygous</td>
<td>PATHOGENIC</td>
</tr>
<tr>
<td>MUTYH</td>
<td>c.536A&gt;G (p.Tyr179Cys)</td>
<td>heterozygous</td>
<td>PATHOGENIC</td>
</tr>
</tbody>
</table>

About this test
This diagnostic test evaluates 47 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.
# Potential Germline Testing Outcomes

| Pathogenic/Likely Pathogenic | • Variant associated with disease  
|                            | • Follow management recommendations for pathogenic variant detected  
|                            | • Offer cascade testing to at risk relatives |
| Variant of Uncertain Significance | • Variant not actionable; Inadequate information on impact of germline variant on disease  
|                                | • Manage patient on personal and family cancer history  
|                                | • Do not test family members for variant |
| Negative                       | • Manage patient based upon personal and family cancer history |
Case 1. Management of patient and family

• Endoscopic surveillance of remaining colorectum and UGI tract
• Offer at risk relatives testing of family MUTYH pathogenic variant
  • Follow MAP management recommendations for bi-allelic PV carriers
  • For mono-allelic PV carriers with first degree relative with CRC:
    • Colonoscopy every 5 years beginning age 40 or 10 years prior to age of first degree relative with CRC, whichever is earlier
Adenomatous Polyposis Syndromes

Familial Adenomatous Polyposis (FAP)
- Autosomal Dominant
- Pop prevalence: 1:10,000 individuals
- Due to PV in APC gene
  - Tumor suppressor gene
  - 30% cases are de novo
- Risk of CRC: 60-90%
  - Based on polyposis burden
- Risk of extra-colonic tumors

MUTYH Associated Polyposis (MAP)
- Autosomal recessive
- Pop prevalence: 1-2% mono-allelic carriers of PV in MUTYH
- Due to bi-allelic PV in MUTYH gene
  - Base excision repair gene
- Risk of CRC: 50% @ 48 yrs
  - Attenuated colorectal polyposis
- Spectrum of extra-colonic tumors similar to FAP but milder and less prevalent
Features of FAP (MAP)

- CRC and polyposis
- Gastric polyposis and cancer
- Duodenal polyposis and cancer
- Desmoid tumors (15%)
- Thyroid carcinoma (2-17%)
- Adrenal adenoma (7-13%)
- Osteomas (50-90%)
- Supernumerary teeth (11-27%)
- CHRPE (70-80%)
- Soft tissue tumors (50%)
  - Lipoma, fibroma, sebaceous cysts
- Hepatoblastoma (<2%)
Gastric features of FAP/MAP

- Fundic gland polyposis
  - Prevalence: 88%
  - 50% with low grade foveolar dysplasia
  - 3% HGD

Gastric Cancer in FAP

- 767 patients with > 1 EGD between 2001-2016
- 1 case between 1979 and 2006
- 9 cases diagnosed between 2012-2016
- Mean age 57 years (35-75 yrs)
- Prevalence: 1.3%; Standardized incidence ratio of 140
- All in proximal stomach, unifocal
- 60% Stage IV and died of disease within months

Mankaney G, Familial Ca 2017:16:371
Endo-Pathologic Features of Gastric Cancer Risk

### Table 1. Comparison of Gastric Endoscopic Findings

<table>
<thead>
<tr>
<th>Feature</th>
<th>FAP Patients with WMP</th>
<th>FAP Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpeting of proximal polyps</td>
<td>100%</td>
<td>26%</td>
</tr>
<tr>
<td>Polypoid mounds</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>Solitary polyps &gt; 1 cm</td>
<td>57%</td>
<td>16%</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of Gastric Histologic Findings

<table>
<thead>
<tr>
<th>Feature</th>
<th>FAP Patients with WMP</th>
<th>FAP Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundic Gland Polyp - No Dysplasia</td>
<td>2 (14.2%)</td>
<td>12 (85.7%)</td>
</tr>
<tr>
<td>Fundic Gland Polyp - Low Grade Dysplasia</td>
<td>13 (92.8%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Fundic Gland Polyp - High Grade Dysplasia</td>
<td>3 (21.4%)</td>
<td>4 (28.5%)</td>
</tr>
<tr>
<td>Tubular Adenoma</td>
<td>4 (28.5%)</td>
<td>4 (28.5%)</td>
</tr>
<tr>
<td>Pyloric Gland Adenoma</td>
<td>2 (14.2%)</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0</td>
<td>2 (14.2%)</td>
</tr>
</tbody>
</table>

Das Kunnathu N, GIE 2018;88(3):569-570
Endoscopic Findings in Proximal Polyposis

- Consensus criteria were developed based on 128 low-risk and 22 high-risk polyps
- Using the surface morphology criteria, 5 endoscopists distinguished high- from low-risk polyps with sensitivity and specificity of 79% each.
- The k coefficient was .45

Mankaney G, Gastrointest Endosc. 2020 Sep;92(3):755-762
Duodenal features of FAP

• Duodenal adenomas
  • Prevalence: 100%

• Adenomatous papilla
  • 54% if papilla appears normal
  • 89% if papilla appears abnormal

• Periampullary/Duodenal cancer
  • Prevalence: 2-36%
  • Cancer risk greatest in Stage VI duodenal polyposis
    • Nearly half of patients with duodenal cancer did not have Stage IV duodenal polyposis

1Burke C, GIE 1999;49:358
2Groves C Gut 2002;50:636
3Thiruvengadam S, Gastrointest Endosc. 2019 Feb;89(2):345-354
## Staging of Duodenal Polyposis

<table>
<thead>
<tr>
<th></th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of polyps</td>
<td>1-4</td>
<td>5-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Polyp size (mm)</td>
<td>1-4</td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Histology</td>
<td>Tubular</td>
<td>TVA</td>
<td>Villous</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Spigelman AD. Lancet 1989;2: 783

<table>
<thead>
<tr>
<th>Stage</th>
<th>Points</th>
<th>10 yr Cumulative Cancer Risk</th>
<th>Surveillance: EGD with Evaluation of Papilla</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1-4</td>
<td>0%</td>
<td>FAP: 20-25 yrs</td>
</tr>
<tr>
<td>II</td>
<td>5-6</td>
<td>2.3%</td>
<td>MAP: 30-35 yrs</td>
</tr>
<tr>
<td>III</td>
<td>7-8</td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>9-12</td>
<td>36%</td>
<td>Consider Duodenectomy; Expert EGD Q 3-6 months</td>
</tr>
</tbody>
</table>

FAP/MAP Polyposis Surgery

• Required if symptoms, advanced adenomas or excess or progressive polyp burden

• Need to know rectal polyp burden and desmoid risk

• Operations
  - Total colectomy and ileorectal anastomosis (IRA)
  - Proctocolectomy and ileal pouch anal anastomosis
## Surveillance of FAP/MAP

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Procedure</th>
<th>Age (yrs)</th>
<th>Interval (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic FAP</td>
<td>Colonoscopy preferred Over FS</td>
<td>10-15</td>
<td>1 year</td>
</tr>
<tr>
<td>aFAP/MAP</td>
<td>Colonoscopy</td>
<td>18-20/25-30</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td>Surgical Consult</td>
<td>When polyps detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post operative</td>
<td>FS or pouchoscopy</td>
<td>NA</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroid Ultrasound</td>
<td>Late teens</td>
<td>2-5 yrs if normal</td>
</tr>
</tbody>
</table>

NCCN guidelines Genetic/Familial High Risk Assessment Colorectal. 2021
Feng X, et al Thyroid. 2015;Mar;25(3):325-32. PMID: 25585202
### Colonic Polyposis of Unknown Etiology

Cumulative History of >10-20 adenomas and Negative Multi-Gene panel testing

<table>
<thead>
<tr>
<th>Phenotype (based on cumulative lifetime adenomas)</th>
<th>Management/Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of ≥100 adenomas</td>
<td>Manage as FAP (See FAP-1)</td>
</tr>
</tbody>
</table>
| Personal history of 20–<100 adenomas: Adenoma burden that cannot be managed endoscopically | • Surgical evaluation and counseling if appropriate  
• Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater)² and repeat following duodenal surveillance guidelines on page FAP-B. |
| Personal history of 20–<100 adenomas: Adenoma burden manageable by colonoscopy and polypectomy | • High-quality colonoscopy and polypectomy every 1–2 years  
› At minimum, clearing of all polyps (≥2 mm) is recommended. Repeat at short interval if residual polyps are present.  
› Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater)² and repeat following duodenal surveillance guidelines on page FAP-B.  
› Surgical evaluation may be considered if polyps not manageable or based on patient preference |
| Personal or family history of 10–19 adenomas | Manage based on clinical judgment. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy, with more frequent surveillance favored for younger age at meeting threshold or higher adenoma burden at last colonoscopy. See NCCN Guidelines for Colorectal Cancer Screening |
| Family history of ≥100 adenomas in a first-degree relative⁴,⁵ AND meets one of the following criteria:  
1) Family member tested, with no pathogenic variant identified; OR  
2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified | • High-quality colonoscopy every 12 mo beginning at age 10–15 y. In some families, based on clinical judgment, initiating colonoscopy beginning in late teens, then every 2 y may be appropriate.  
› If no adenomas, then can lengthen interval to every 2 y. If multiple surveillance exams without adenomas on follow-up, may lengthen interval further based on clinical judgment.  
› If ≥100 adenomas found, manage based on Classical FAP Treatment and Surveillance: Personal History (See FAP-1) or  
› If <100 adenomas found, manage based on AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (See AFAP-1) |
| Family history of 20–<100 adenomas in a first-degree relative⁴,⁵ AND meets one of the following criteria:  
1) Family member tested, with no pathogenic variant identified; OR  
2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified | • High-quality colonoscopy beginning in late teens, then every 2 y. Initial initiation age and frequency of colonoscopy may be modified based on clinical judgment. If multiple surveillance exams without adenomas on follow-up, may lengthen interval further based on clinical judgment.  
› If adenomas found, manage based on AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (See AFAP-1) |

NCCN guidelines Genetic/Familial High Risk Assessment Colorectal. 2021
Conclusions

• Hereditary adenomatous polyposis syndromes are not rare
  • > 10% in individuals with 10-19 lifetime cumulative adenomas

• FAP and MAP are the most common hereditary adenomatous syndromes
  • Gastroenterologist are key in management of these syndromes

• Germline testing indicated
  • > 10-20 cumulative lifetime adenomas
  • If known PV in family
  • Test affected patient first, then family members when PV detected
  • If no affected relative consider germline testing in at risk individual

• Multi-gene panel testing
  • Consider where more than one syndrome possible
  • Broadening the clinical phenotype of CRC
    • At least 30% of patients with germline PV did not meet classic criteria for that syndrome