IDENTIFYING AND MANAGING HEREDITARY ADENOMATOUS POLYPOSIS SYNDROMES
DISCLAIMER

- This information is provided to help answer questions with respect to polyposis and colon cancer risks, hereditary cancer risks and predispositional cancer testing. It is general in nature and is not intended to provide a comprehensive, definitive analysis of specific risk factors for cancer or hereditary cancer risks. The information provided herein should not be relied upon; but rather, should be taken into consideration with other medical and research information regarding cancer risks, hereditary cancer risks and pre-dispositional cancer testing and risk factors.

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AT THE CONCLUSION OF THIS PRESENTATION, PARTICIPANTS SHOULD UNDERSTAND THE FOLLOWING RELATING TO HEREDITARY ADENOMATOUS POLYPOSIS SYNDROMES:

- Clinical features of hereditary adenomatous polyposis syndromes
  - Familial Adenomatous Polyposis (FAP)
  - Attenuated Familial Adenomatous Polyposis (AFAP)
  - MYH-Associated Polyposis (MAP)
- Indications for consideration of genetic testing
- Medical management options
- Appropriate interpretation of genetic test results
COLORECTAL POLYPS

- ~50% of adults will be found to have at least one colorectal polyp during their lifetime
- ~30% of adults will be found to have at least one colorectal adenoma during their lifetime
  - Colorectal adenomas are “precancerous polyps” which have the potential to develop into invasive colorectal adenocarcinoma
HEREDITARY COLORECTAL CANCER: ADENOMATOUS POLYPOSIOS SYNDROMES

- The majority of hereditary colorectal adenomatous polyposis is caused by mutations in one of two genes
  - APC
  - MYH

- The conditions associated with mutations in these genes include:
  - Familial Adenomatous Polyposis (FAP)
  - Attenuated Familial Adenomatous Polyposis (AFAP)
  - MYH-Associated Polyposis (MAP)
PREVALENCE OF FAP AND MAP IN COLORECTAL CANCER

- Up to 1% of all colorectal cancer is due to FAP
- Approximately 1% of colorectal cancer and up to 3% of early onset colorectal cancer is due to MAP
MUTATION IDENTIFICATION IN PATIENTS WITH AFAP AND MAP

- APC germline mutations
  - Account for up to 85-90% of clinically diagnosed FAP
  - Account for up to 30% of clinically diagnosed AFAP
- Biallelic MYH germline mutations
  - Account for ~15-30% of adenomatous polyposis patients who are negative upon APC mutation analysis.
MAP - MUTATION SPECTRUM

- Two founder mutations in Caucasian Northern European population
  - Y165C and G382D
  - Account for 73% of MYH mutations in the Northern European population
- There are common mutations in individuals of varied ethnicities including individuals of East Indian, Pakistani, Japanese, Italian, Finnish, and Portuguese ancestry
IDENTIFYING PATIENTS AT RISK FOR HEREDITARY ADENOMATOUS POLYPOSIS SYNDROMES
MEDICAL SOCIETY STANDARDS AND GUIDELINES

- ACCC- Association of Community Cancer Centers
- AMA- American Medical Association
- ASCRS- American Society of Colon and Rectal Surgeons
- AGA- American Gastroenterological Association
- ASCO- American Society of Clinical Oncology
- NCCN- National Comprehensive Cancer Network
- ONS- Oncology Nursing Society
- SSO- Society of Surgical Oncology
- NSGC- National Society of Genetic Counselors
"RED FLAGS" FOR ADENOMATOUS POLYPOsis SYNDROMES

- ≥10 cumulative colorectal adenomas
- Colorectal cancer associated with multiple adenomas
- Previously identified adenomatous polyposis mutation(s) in the family

Red Flags identify patients at risk for hereditary adenomatous polyposis syndromes for whom further clinical evaluation to determine appropriateness of genetic testing is warranted.

Assessment criteria based on medical society guidelines. For these individual medical society guidelines, go to www.myriadpro.com/guidelines
CLINICAL FEATURES OF ADENOMATOUS POLYPOSIС SYNDROMES
### ADENOMATOUS POLYPOSIS SYNDROMES

<table>
<thead>
<tr>
<th>CONDITION:</th>
<th>FAP</th>
<th>AFAP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENE:</strong></td>
<td>APC</td>
<td>APC</td>
<td>MYH</td>
</tr>
<tr>
<td><strong>INHERITANCE PATTERN:</strong></td>
<td>Autosomal Dominant</td>
<td>Autosomal Dominant</td>
<td>Autosomal Recessive</td>
</tr>
<tr>
<td><strong>ADENOMA NUMBER:</strong></td>
<td>100 or more, sometimes 1000s</td>
<td>0 to hundreds</td>
<td>0 to hundreds</td>
</tr>
<tr>
<td><strong>ADDITIONAL INFORMATION</strong></td>
<td>20-30% of cases will be first affected individual in family</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Variable presentation and clinical overlap necessitates testing for all three conditions.
ADENOMATOUS POLYPOSIOSIS SYNDROMES INCREASE COLORECTAL CANCER RISK

Risk of Cancer (%)

- General Population
- AFAP & MAP
- FAP

CRC by age 70

- Up to 80%
- >99%
- 2%

Cancer Epidemiol Biomarkers Prev 2006 Feb;15(2)
# Familial Adenomatous Polyposis

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Duodenal/periampullary</td>
<td>4-12%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Gastric</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Adrenal</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>CNS (most often medulloblastoma)</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>1.6% (to age 5)</td>
</tr>
</tbody>
</table>
# Familial Adenomatous Polyposis

## Additional Extra-Colonic Risks

<table>
<thead>
<tr>
<th>Condition</th>
<th>Lifetime Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundic gland polyps of the stomach</td>
<td>26-61%</td>
</tr>
<tr>
<td>Desmoid tumors</td>
<td>15%</td>
</tr>
<tr>
<td>Duodenal adenomas</td>
<td>80-100%</td>
</tr>
<tr>
<td>Osteomas (1-2% in general population)</td>
<td>20%</td>
</tr>
<tr>
<td>Dental abnormalities (supernumerary or impacted teeth)</td>
<td>17%</td>
</tr>
<tr>
<td>Cutaneous findings: epidermal cysts, fibromas, lipomas, leiomyomas, neurofibromas, pigmented skin lesions</td>
<td>Up to 50%</td>
</tr>
<tr>
<td>CHRPE (congenital hypertrophy of the retinal pigmented epithelium)</td>
<td>20%</td>
</tr>
</tbody>
</table>

*GUT* 2004 December;53(12):1832-1836.
MYH-ASSOCIATED POLYPOSIS

LIFETIME CANCER RISKS

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>≥80%</td>
</tr>
<tr>
<td>Duodenal/periampullary</td>
<td>~4%</td>
</tr>
<tr>
<td>Sebaceous gland tumors</td>
<td>~2%</td>
</tr>
</tbody>
</table>

- FAP-like features
  - Duodenal polyposis present in ~17% of MAP patients
  - Incidence of other FAP-like features appears to be low and mainly described as part of case reports
MANAGING HEREDITARY CANCER RISKS
MANAGING CANCER RISK IN ADENOMATOUS POLYPOSIS SYNDROMES

Markedly improved outcomes with proven medical interventions

- Surveillance
- Chemoprevention
- Surgery

Any discussion of medical management options is for general informational purposes only and does not constitute a recommendation. While genetic testing and medical society guidelines provide important and useful information, medical management decisions should be made based on consultation between each patient and his or her healthcare provider.

Gastroenterology 2001;121:198-213.
<table>
<thead>
<tr>
<th>SITE</th>
<th>PROCEDURE</th>
<th>AGE TO BEGIN</th>
<th>INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>Sigmoidoscopy or Colonoscopy</td>
<td>10-15 years</td>
<td>Annually (Until polyps develop and surgery is indicated)</td>
</tr>
<tr>
<td>AFAP</td>
<td>Colonoscopy</td>
<td>15-20 years</td>
<td>1-3 years (Interval based on adenoma burden)</td>
</tr>
</tbody>
</table>
# FAP/AFAP - EXTRA-COLONIC SCREENING

<table>
<thead>
<tr>
<th>CANCER RISK</th>
<th>SCREENING</th>
<th>AGE AND INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal, gastric, peri-ampullary</td>
<td>Upper GI endoscopy with end and side-viewing examination</td>
<td>Begin age 25-30 Repeat every 1-3 yrs</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Consider small bowel visualization</td>
<td>Initiate depending on duodenal polyp status</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroid exam/ultrasound</td>
<td>Begin late teens Annual</td>
</tr>
<tr>
<td>CNS</td>
<td>Physical examination</td>
<td>Annual</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>Consider AFP, hepatic ultrasound, liver palpation</td>
<td>Every 3-6 months First 5 years of life</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>No current recommendations</td>
<td></td>
</tr>
</tbody>
</table>
ADENOMATOUS POLYPOSIS CHEMOPREVENTION

- Chemoprevention options have been studied in efforts to reduce polyp burden
  - COX-2 inhibitors, aspirin, curcumin and resistant starch have all been investigated for possible impact on polyp development
- Consider enrollment in clinical trials
ADENOMATOUS POLYPOSIS
SURGICAL GUIDELINES

- FAP (severe polyposis)
  - Colectomy or proctocolectomy
  - Optional post surgical chemoprevention
  - Post-surgery surveillance for rectal and extracolonic tumors
- AFAP (less severe polyposis)
  - Colectomy is eventually necessary in approximately two-thirds of individuals, dependent on the polyp burden
## MAP MEDICAL MANAGEMENT OPTIONS

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Surveillance</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Colorectal Surgical Management</td>
<td>Consideration of colectomy or proctocolectomy</td>
</tr>
<tr>
<td>Duodenal Surveillance</td>
<td>Consider upper endoscopy with side viewing duodenoscopy</td>
</tr>
</tbody>
</table>

- Colonoscopy: Begin at 25-30 years every 1-5 years (interval based upon polyp burden)
- Surgical options should be based upon adenoma burden
- Begin at 30-35 years every 3-5 years
GENETIC TESTING STRATEGY FOR ADENOMATOUS POLYPOSIS SYNDROMES
ADENOMATOUS POLYPOSES
GENETIC TESTING STRATEGIES

- APC full sequencing and large rearrangement analysis and MYH mutations Y165C and G382D
  - Patients identified with one MYH mutation proceed automatically to full sequencing of MYH
- Consider full sequencing of MYH for patients negative for Y165C and G382D mutations
  - Up to 22% of biallelic MYH carriers do not have either N. European founder mutation
  - Multiple other common mutations in other ethnicities
INTERPRETING AND UTILIZING TEST RESULTS IN MEDICAL MANAGEMENT
INTERPRETING GENETIC TEST RESULTS

- Positive for deleterious mutation(s)
- No mutation detected
  - Mutation(s) previously identified in the family
  - No known mutation in the family
- Genetic variant of uncertain clinical significance
POSITIVE FOR DELETERIOUS MUTATION(S)  
FAP AND AFAP

- Syndrome-associated cancer risks
- Relatives at risk
  - 50% chance for first degree relatives (children, siblings, parents) to inherit the mutation
- Consider testing at-risk relatives for identified familial mutation(s)
POSITIVE FOR DELETERIOUS MUTATION(S) BIALLELIC MYH

- Syndrome-associated cancer risks
- Relatives at risk
  - 25% chance for siblings to inherit both mutations
- Consider testing at-risk relatives for identified familial mutation(s)
NO MUTATION DETECTED

No known family mutation
- Rules out most causes of hereditary polyposis
- Manage based on the negative result and personal and family cancer/adenoma history

Negative for known family mutation(s)
- General population cancer/adenoma risks – if no history on the other side of the family
- Avoid unnecessary screening/surgery
GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE

- Clinical significance not yet known
- Manage based on personal & family cancer/adenoma history
- May be further clarified by:
  - testing of specified family members
  - molecular or functional analysis
  - population studies
IN SUMMARY:

1. Screen for “Red Flags”
   - ≥10 cumulative colorectal adenomas
   - Colorectal cancer associated with multiple adenomas
   - Previously identified adenomatous polyposis mutation(s) in the family

2. Discuss genetic testing options, if appropriate

3. Establish appropriate medical management plan
KNOWLEDGE IS POWER... AND HOPE.
SUPPLEMENTAL SLIDES
BENEFITS AND LIMITATIONS OF GENETIC TESTING

- **Benefits**
  - Allows for a specific genetic diagnosis, which results in individualized medical management
  - Accurate risk assessment
  - Alleviates uncertainty and anxiety

- **Limitations**
  - Genetic testing does not identify all causes of hereditary colorectal cancer
GENETIC DISCRIMINATION
MYTH VERSUS REALITY

- Federal and state laws prohibit the use of genetic information as a ‘pre-existing condition’
  - Federal HIPAA legislation
  - The majority of states have additional laws
  - Genetic Information Nondiscrimination Act (GINA)
ADENOMA NUMBER IN ADENOMATOUS POLYPOSIS SYNDROMES

AFAP  MAP  FAP
0 adenomas  100 adenomas  1000 adenomas

Gastroenterology 2004;127:9-16.

Myriad Genetic Laboratories, Inc. ©2011
DISTINGUISHING BETWEEN AFAP/MAP AND LYNCH SYNDROMES

<table>
<thead>
<tr>
<th></th>
<th>LYNCH SYNDROME</th>
<th>AFAP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene:</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>APC</td>
<td>MYH</td>
</tr>
<tr>
<td>Inheritance:</td>
<td>Autosomal Dominant</td>
<td>Autosomal Dominant</td>
<td>Autosomal Recessive</td>
</tr>
<tr>
<td>Polyp Number:</td>
<td>Typically less than 10</td>
<td>0-99</td>
<td>0-1000</td>
</tr>
<tr>
<td>Colorectal Cancer Risk:</td>
<td>~ 80% by age 70</td>
<td>greater than 80%</td>
<td></td>
</tr>
</tbody>
</table>

- Similar cancer spectrum: AFAP, MAP and Lynch
- Right sided colon cancers favored
- MAP and Lynch colorectal cancers can present with similar MSI pathology
COLORECTAL CANCER SYNDROMES ASSOCIATED WITH POLYPS

- Adenomatous polyposis syndromes
  - Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)
  - MYH-Associated Polyposis (MAP)
- Hamartomatous polyposis syndromes
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - Cowden syndrome
- Mixed polyposis and other rare syndromes
FAP/AFAP - DE NOVO MUTATIONS

- Up to 30% of individuals with APC mutations have de novo mutations – neither parent is found to have the mutation
- De novo mutation assumed to have occurred during formation of the germ cell
- Somatic mosaicism (mutation occurs in early embryo leading to two cells lines) accounts for up to 20% of de novo cases – variable phenotype
# Colorectal Cancer Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Sporadic</th>
<th>Lynch Syndrome</th>
<th>MAP</th>
<th>AFAP</th>
<th>FAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyps</strong></td>
<td>few</td>
<td>few</td>
<td>0-1000</td>
<td>0-99</td>
<td>≥100</td>
</tr>
<tr>
<td><strong>CRC Risk</strong></td>
<td>2%</td>
<td>Up to 82%</td>
<td>Up to 80%</td>
<td>Up to 80%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td><strong>Gene(s)</strong></td>
<td>-</td>
<td><strong>MLH1, MSH2, MSH6, PMS2, EPCAM</strong></td>
<td><strong>MYH</strong></td>
<td><strong>APC</strong></td>
<td><strong>APC</strong></td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>Colonoscopy 50y Every 10 yrs</td>
<td>Colonoscopy 20-25y Every 1-2 yrs</td>
<td>Colonoscopy 25-30y Every 1-5 yrs</td>
<td>Colonoscopy 15-20y Every 1-3 yrs</td>
<td>Flex Sig or Colonoscopy 10-15y Annually</td>
</tr>
<tr>
<td><strong>Surgical Options</strong></td>
<td>Based on tumor size/location</td>
<td>Hemicolecotomy or colectomy w/ IRA</td>
<td>Based on polyp burden</td>
<td>Based on polyp burden</td>
<td>Colectomy or proctocolectomy</td>
</tr>
</tbody>
</table>
DOMINANT VS RECESSIVE INHERITANCE

DOMINANT INHERITANCE
- A mutation in only one copy of the gene causes disease
- Each child of an affected parent has a 50% risk of inheriting the mutation

RECESSIVE INHERITANCE
- A mutation in both copies of the gene required for disease risk
- Both parents must be "carriers" of a mutation to have an affected child
  - Each child has a 25% risk of disease

Mutation → Disease

Mutation
No Disease

Mutation
Mutation → Disease