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.

Personal and Non-Commercial Use

- The hereditary polyposis slides are for your personal and non-commercial use. You may not modify, publish, reproduce license, create derivative works from or sell any information obtained from the hereditary colon cancer slides.

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

Gastrointest Endosc 2009;70:1182.99
Clin Gastroenterol Hepatol 2009;7:1272-78

HEREDITARY COLORECTAL CANCER: ADENOMATOUS POLYPOSIS 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)

Gastroenterol 2010;138:2044-58.

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

Am J Gastroenterol 2006;101:385-98.
Gastroenterology 2009;136:1251-60.
Clin Cancer Res 2010;16:5402-13.

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.

Fam Cancer 2006;5:221-6.
Clin Genet 2007;71:427-33.
Ann Surg 2006;244:874-880.
Crit Rev Oncol Hematol 2011;79:1-16.

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

Surg Oncol Clin N Am. 2009; 18: 687-703.
Gastro. 2009; 136: 471-6.

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 POLYPOSIS SYNDROMES

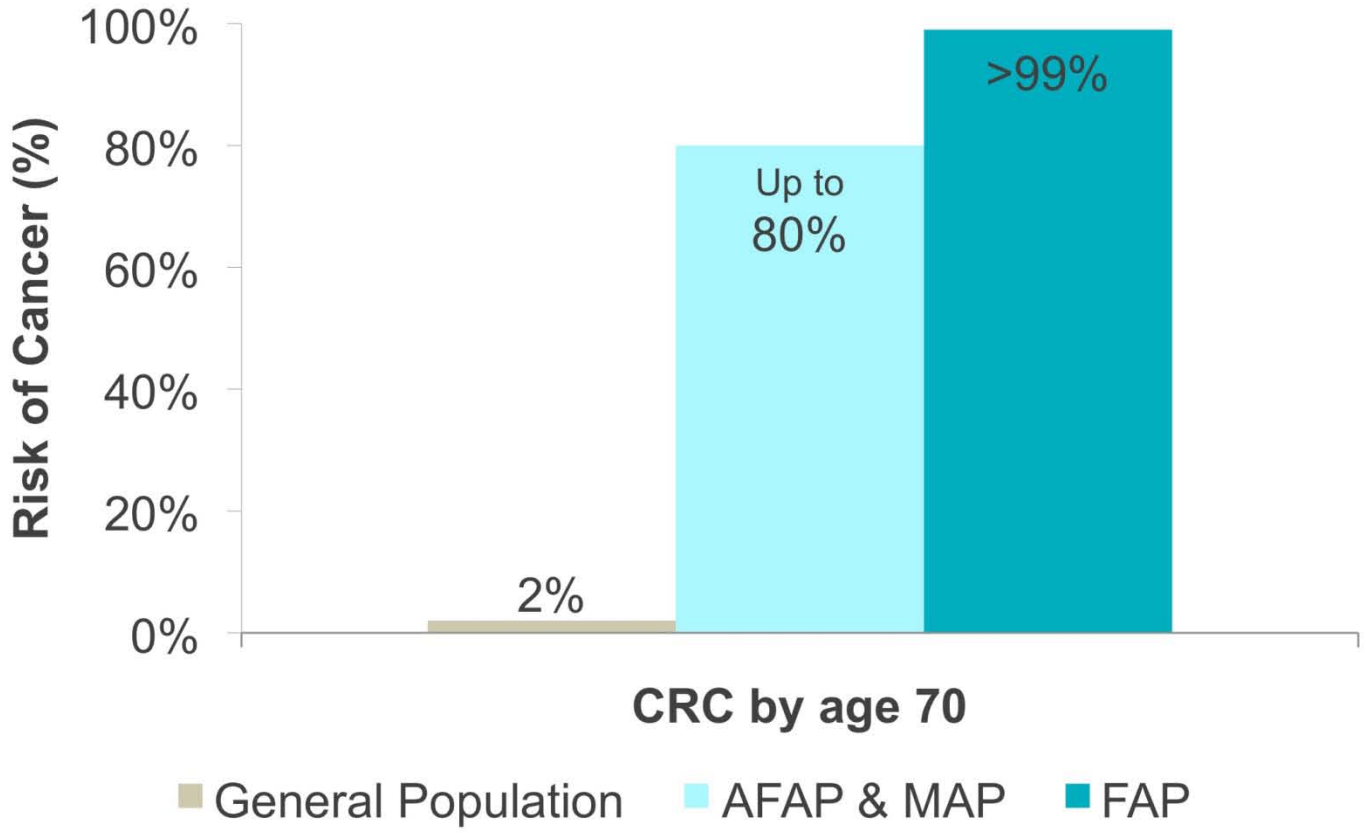
ADENOMATOUS POLYPOSIS SYNDROMES VARIABLE PRESENTATIONS

CONDITION:	FAP	AFAP	MAP
GENE:	*APC*	*APC*	*MYH*
INHERITANCE PATTERN:	Autosomal Dominant	Autosomal Dominant	Autosomal Recessive
ADENOMA NUMBER:	100 or more, sometimes 1000s	0 to hundreds	0 to hundreds
ADDITIONAL INFORMATION	20-30% of cases will be first affected individual in family		

- Variable presentation and clinical overlap necessitates testing for all three conditions

Am J Gastroenterol 2006
Surg Onc Clin N Am 2009

ADENOMATOUS POLYPOSIS SYNDROMES INCREASE COLORECTAL CANCER RISK



Textbook of Gastroenterology. Philadelphia Lippencott Williams and Wilkins 2003:1920.
Cancer Epidemiol Biomarkers Prev 2006 Feb;15(2)
Am J Gastroenterol. 2006 Feb;101(2):385-98.

FAMILIAL ADENOMATOUS POLYPOSIS

LIFETIME CANCER RISKS	
	Lifetime Risk
Colorectal	>99%
Duodenal/periampullary	4-12%
Thyroid	<2%
Gastric	<2%
Pancreatic	<2%
Adrenal	<2%
CNS (most often medulloblastoma)	<2%
Hepatoblastoma	1.6% (to age 5)

Am J Gastroenterol. 2006 Feb; 101(2):385-98.
Curr Mol Med. 2007 Feb;7(1):29-46.

FAMILIAL ADENOMATOUS POLYPOSIS

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

Am J Gastroenterol. 2006 Feb;101(2):385-98.
GUT 2004 December;53(12)1832-1836.
Ann Surg Oncol. 2008 September; 15(9): 2439–2450.

MYH-ASSOCIATED POLYPOSIS

LIFETIME CANCER RISKS	
Colorectal	≥80%
Duodenal/periampullary	~4%
Sebaceous gland tumors	~2%

- 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

Cancer Epidermiol Biomarkers. 2006; 15 (2).
Gastro. 2009; 137 (6): 1-10.
Critical Reviews in Oncology Hematology. 2011; 79 (1); 1-16.

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.

Dis Col Rect 1993;36:1059-62.
Scand J Gastroenterol 2000;35:1284-7.
Gastroenterology 2001;121:198-213.

SURVEILLANCE GUIDELINES COLON AND RECTUM

SITE	PROCEDURE	AGE TO BEGIN	INTERVAL
FAP	Sigmoidoscopy or Colonoscopy	10-15 years	Annually (Until polyps develop and surgery is indicated)
AFAP	Colonoscopy	15-20 years	1-3 years (Interval based on adenoma burden)

Am J Gastroenterol. 2006 Feb;101(2):385-98.
www.nccn.org

FAP/AFAP - EXTRA-COLONIC SCREENING

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

www.NCCN.org

Pediatr Blood Cancer. 2006 Nov;47(6):811-8.

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

Familial Cancer 2008:7;59-64.
Cancer Prev Res; 4(5); 655–65. 2011 AACR
www.NCCN.org

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

Diseases of the Colon & Rectum 2003;46:1001-12.
American Journal of Gastroenterology. 2006:101:385-398.
J Clin Oncol. 2006 Oct 1;24(28):4642-60.
www.nccn.org

MAP MEDICAL MANAGEMENT OPTIONS

	PROCEDURE	AGE
Colorectal Surveillance	Colonoscopy	Begin at 25-30 years every 1-5 years (interval based upon polyp burden)
Colorectal Surgical Management	Consideration of colectomy or proctocolectomy	Surgical options should be based upon adenoma burden
Duodenal Surveillance	Consider upper endoscopy with side viewing duodenoscopy	Begin at 30-35 years every 3-5 years

GENETIC TESTING STRATEGY FOR ADENOMATOUS POLYPOSIS SYNDROMES

ADENOMATOUS POLYPOSIS 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

Surg Oncol Clin N Am. 2009; 18: 687-703.

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

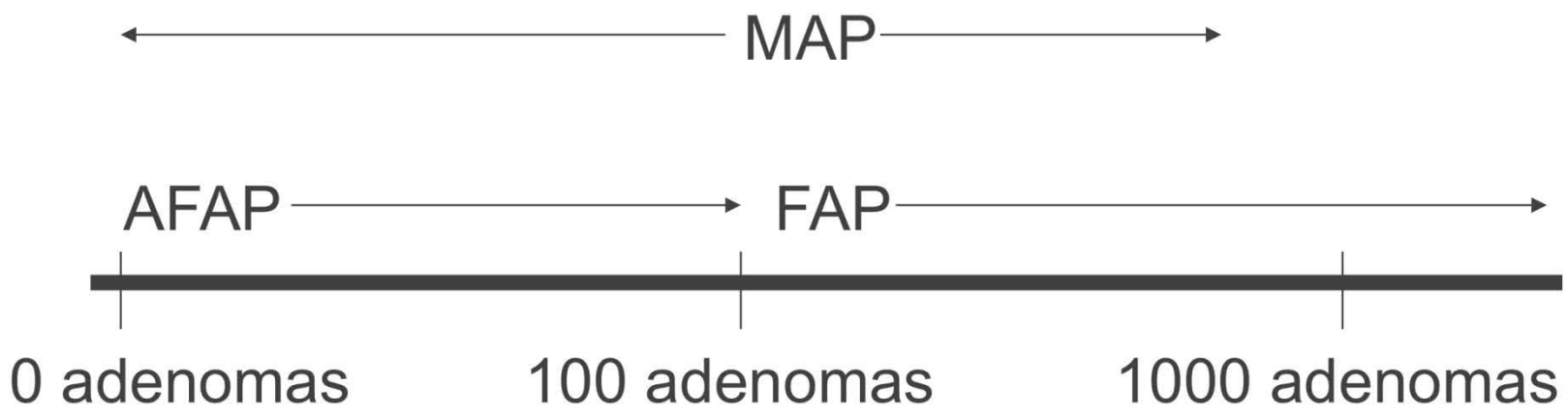
- Benefits
  - Allows for a specific genetic diagnosis, which results in individualized medical management
  - Accurate risk assessment
  - Alleviates uncertainty and anxiety
- Limitations
  - Genetic testing does not identify all causes of hereditary colorectal cancer

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)

AJHG 2000;66:293-307

ADENOMA NUMBER IN ADENOMATOUS POLYPOSIS SYNDROMES



Gastroenterology 2001;121:195-7.
NEJM 2003;348:791-99 .
Gastroenterology 2004;127:444-51.
Gastroenterology 2004;127:9-16.

DISTINGUISHING BETWEEN AFAP/MAP AND LYNCH SYNDROMES

	LYNCH SYNDROME	AFAP	MAP
Gene:	*MLH1, MSH2, MSH6, PMS2, EPCAM*	*APC*	*MYH*
Inheritance:	Autosomal Dominant	Autosomal Dominant	Autosomal Recessive
Polyp Number:	Typically less than 10	0-99	0-1000
Colorectal Cancer Risk:	~ 80% by age 70	greater than 80%	

- Similar cancer spectrum: AFAP, MAP and Lynch
- Right sided colon cancers favored
- MAP and Lynch colorectal cancers can present with similar MSI pathology

Critical Reviews In Oncology Hematology 2010.
Gastroenterology 2004;127:444-451.

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

Human Mutation 1994. 3: 121-5.
Gut 2008; 57: 71-76.

COLORECTAL CANCER COMPARISONS

	SPORADIC	LYNCH SYNDROME	MAP	AFAP	FAP
POLYPS	few	few	0-1000	0-99	≥100
CRC RISK	2%	Up to 82%	Up to 80%	Up to 80%	>99%
GENE(S)	-	*MLH1, MSH2, MSH6, PMS2, EPCAM*	*MYH*	*APC*	*APC*
SCREENING	Colonoscopy 50y Every 10 yrs	Colonoscopy 20-25y Every 1-2 yrs	Colonoscopy 25-30y Every 1-5 yrs	Colonoscopy 15-20y Every 1-3 yrs	Flex Sig or Colonoscopy 10-15y Annually
SURGICAL OPTIONS	Based on tumor size/ location	Hemicolectomy or colectomy w/ IRA	Based on polyp burden	Based on polyp burden	Colectomy or procto-colectomy

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