

MEETING ABSTRACTS

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## ORAL PRESENTATIONS

### O1

#### Mutation-negative FAP patients with mRNA defects of APC

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*Hereditary Cancer in Clinical Practice* 2010, **8**(Suppl 1):O1

**Background:** Familial adenomatous polyposis (FAP) is a colon cancer syndrome with a prevalence of 1:10,000, hallmarked by 100s to 1000s of precancerous colonic polyps and nearly 100% lifetime risk of developing colon cancer at an average age of 39 years in the absence of colon surveillance and surgery. Mutations in the APC gene lead to FAP or an attenuated form called AFAP with reduced polyp numbers and cancer risk. Mutation detection fails using DNA based technology in 20% of FAP and 50% of AFAP patients due to testing limitations, inability to determine significance of DNA change, or other responsible genes. A subset of disease causing APC mutations may be due to non-coding or even coding variants that result in RNA splice defects.

**Methods:** A RNA-based assay has been developed to screen APC mRNA for splice defects in mutation-negative FAP and AFAP patients. Primers and PCR conditions were developed for five overlapping amplicons that cover exons 1-14 and the beginning of exon 15 in the APC mRNA. PCR products from the cDNA of patients were run on agarose gels and examined for atypical products.

**Results:** To date, cDNA from 14 mutation-negative families has been tested, and two mutations resulting in splice defects have been identified when other standard techniques failed to demonstrate loss-of-function mutations. One is a single nucleotide change, deep in intron 4 that generates a splice acceptor site, an additional exon (exon 4A), that includes a new stop codon. The second is a 1.5-kb deletion in intron 14 which causes deletion of exon 14 in the mRNA transcript; exon 13 is spliced to exon 15, resulting in an out-of-frame stop codon. Both families present as AFAP.

**Conclusions:** This is a useful assay to compliment DNA-based testing in APC mutation-negative patients or patients with a variant of uncertain

significance. Additionally, to address cases where undetected mutations affect the stability of the resultant transcript, allelic imbalance can be examined in amplicons containing one of the common APC single nucleotide polymorphisms (SNPs) using real-time PCR.

**Acknowledgement:** This research was supported by NCI grants PO1-CA073992 (RWB), RO1-CA040641 (RWB) and by the Huntsman Cancer Foundation.

### O2

#### Juvenile Polyps: a large pediatric cohort

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*Hereditary Cancer in Clinical Practice* 2010, **8**(Suppl 1):O2

**Background:** Juvenile polyps, classified as hamartomatous lesions with neoplastic potential, are the most common gastrointestinal polyp of childhood. Risk factors for neoplasia include germline DNA mutations, a family history of juvenile polyps, and multiple polyps ( $\geq 3$  or  $\geq 5$ ). Only a few large pediatric series ( $>100$  patients) of patients with juvenile polyps have been reported, with limited data about repeat surveillance colonoscopy and the incidence of neoplasia. The primary aim of this study was to identify a large cohort of children with one or more juvenile polyps for descriptive analysis of patient demographics, polyp number, location, repeat colonoscopy, and neoplasia.

**Methods:** Juvenile polyp patients were identified by searching a single hospital pathology database from 1990-2009. Medical records were reviewed for each patient including demographics, family history, genetic testing, and colonoscopy and pathology reports noting polyp number, location, and histology. The right colon was defined as proximal to the splenic flexure.

**Results:** A total of 1,667 polyps were identified in 257 children, of which 158(61.5%) were male. Median age at diagnosis was 5.6 yr (IQR: 3.7, 8.8). Germline DNA mutations were identified in 5 of 17(29.4%) patients tested including SMAD4 (n=2), BMPR1A (n=1), PTEN (n=2). 192 patients underwent complete colonoscopy at initial diagnosis, revealing 1 polyp in 117(60.9%)[Group A] and  $>1$  polyp in 75(39.1%)[Group B]. 60(31.2%) patients had  $\geq 3$  polyps and 29(15.1%) patients had  $\geq 5$  polyps. 128(66.7%) patients had polyps limited to the left colon and

8(4.2%) patients had polyps limited to the right colon, 7 of which were single. Group B was more likely than Group A to have a family history of a 1st or 2nd degree relative with polyps (any type) or colon cancer ( $p=0.006$ ) but no significant difference was found between groups for gender, age, or race. 62 of 192 (32.3%) patients underwent repeat surveillance colonoscopy for polyp detection or removal. The number of times procedures were repeated were 2( $n=38$ ), 3( $n=9$ ), 4( $n=11$ ), and 5, 6, 8, 10( $n=1$  for each). 44 of 75(58.7%) subjects with multiple polyps found at initial diagnosis underwent a second colonoscopy during the study period with a median time interval of 23.4 months (95% CI: 14.2, 41.5). Neoplasia was found in 4(1.6%) of 257 patients, three of which were male, including low grade dysplasia in 3 (ages 4.6, 6.9, and 14.6 yr), and adenocarcinoma with local metastases in one 11.8 yr male without prior adenoma. Each of these patients had  $\geq 5$  polyps detected during initial colonoscopy.

**Conclusions:** This largest series to date of children with juvenile polyps confirms previous observations regarding male predominance, early age of presentation, frequency of multiple polyps, and increased risk of neoplasia. The importance of complete colonoscopy is supported by finding isolated right colon polyps. Cancer may evolve in the absence of prior adenoma detection.

### O3

#### Gastrointestinal polyposis and PTEN mutations: an under-acknowledged diagnostic criterion

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Hereditary Cancer in Clinical Practice 2010, 8(Suppl 1):O3

**Background:** The International Cowden Consortium (ICC) created operational diagnostic criteria that specify gastrointestinal (GI) hamartomas as a minor criterion. Previous review of reported case studies found that 35-85% of Cowden syndrome (CS) patients had GI hamartomas. Our goal is to describe the GI phenotype of our PTEN mutation positive (+) series.

**Methods:** Blood was collected for PTEN mutation analysis and medical records were requested to document diagnoses. Patients who are PTEN+ with  $\geq 5$  GI polyps,  $\geq 1$  of which is hyperplastic (hyp) or hamartomatous (ham,  $n=4$ ) or who met relaxed ICC criteria ( $n=118$ ) were analyzed. Upper and lower GI endoscopy and pathology reports were reviewed and findings are reported descriptively. Fisher's 2-tailed exact test and unpaired T-tests were utilized for comparison of PTEN+ patients with and without polyps.

**Results:** Out of 122 PTEN+ patients, 64 underwent  $\geq 1$  endoscopy, and 60(50%) had polyps or colorectal cancer (CRC). Average age at first colonoscopy and upper endoscopy was 37yrs (range: 2-73) and 40 (2-73) respectively. Number of polyps ranged from 1-innumerable. Polyps were found in the colorectum, ileum, duodenum, stomach, and esophagus. Pathology includes serrated adenomas; ham, hyp, adenomatous (ade), and inflammatory polyps; lymphoid aggregates; neuromas; lipomas; and ganglioneuromas. 16 patients had a hyp or ham polyposis mixed with other types of polyps, 13 had purely hyp or ham polyposis, and 6 had ganglioneuromatosis. 8 patients (6.6%) had CRC, 1 of whom did not have colorectal polyposis. One patient had gastric signet ring cell carcinoma in the setting of diffuse mixed hyp and ade polyposis. Polyposis patients were older at the time of study enrollment (mean=41.6yrs) compared to non-polyposis patients (26.7yrs,  $p=0.0001$ ). The most common CS feature in polyposis patients was macrocephaly (70%). When compared to patients without polyps, those with polyps were more likely to have goiter/thyroid nodules ( $p=0.0001$ ), trichilemmomas ( $p=0.0018$ ), and papillomatous papules ( $p=0.0001$ ), but less likely to have breast cancer ( $p=0.0412$ ) and mental retardation/developmental delay ( $p=0.0062$ ).

**Conclusions:** GI polyposis is the second most common CS feature in our series. Inclusion of this manifestation as a major criterion would result in an additional 19 patients (16%) meeting ICC criteria. We propose that the ICC revise their guidelines to include GI polyposis (defined as ganglioneuromatosis, mixed hyp or ham polyposis, ham or hyp polyposis) as a major criterion.

### O4

#### Colorectal adenomas and cancer link to chromosome 13q22.1-13q31.3 in a large family with excess colorectal cancer

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**Background:** Colorectal cancer is the fourth most common type of cancer and the second most common cause of cancer death. Approximately 5% of colon cancers arise in the presence of a clear hereditary cancer condition; however, current estimates suggest that an additional 15-25% of colorectal cancers arise on the basis of unknown inherited factors. Association studies report several low-penetrance genetic variants associated with colon cancer risk. Large families, whereby precise inheritance can be correlated with phenotype, offer another approach to identify moderately penetrant genes and to isolate responsible genetic loci and mutations. The aim of this study was to identify additional genetic factors responsible for colon cancer using large multigenerational pedigrees with excess colorectal cancer.

**Methods:** A large 4-generation kindred with statistical excess colorectal cancer was identified through the Utah Population Database. 47 family members were enrolled and evaluated clinically by colonoscopy. Genome-wide genotyping was done using two sets of genetic markers: 325 short tandem repeat (STR) and the10K Affymetrix SNP array, as well as fine mapping with 5 additional STR markers. Parametric and nonparametric linkage was analyzed using MLINK and GENEHUNTER.

**Results:** A major genetic locus segregating with colonic polyps and cancer in this kindred was identified on chromosome 13q with a nonparametric linkage score of 26.39 (LOD score of 2.99 and  $p=0.0006$ ). The nonrecombinant region spans 21 Mbp and contains 27 RefSeq genes. Sequencing of 7 candidate genes in this region failed to identify a clearly deleterious mutation; however, polymorphisms segregating with the phenotype were identified. Chromosome 13q is commonly gained and over expressed in colon cancers and is correlated with metastasis suggesting the presence of an oncogene. Evaluation of a tumor from a kindred member revealed a gain of 13q as well.

**Conclusions:** This identified region may contain a novel oncogene responsible for colon cancer in a yet to be determined fraction of the colon cancer population. Identification of the precise gene and causative genetic change will be an important next step to understand cancer progression and metastasis.

**Acknowledgment:** This research was funded by NIH grants R01-CA040641 (RWB) and P01-CA07392 and Huntsman Cancer Foundation.

### O5

#### Cancer occurrence during follow-up of the CAPP2 study -aspirin use for up to four years significantly reduces Lynch syndrome cancers for up to several years after completion of therapy

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Hereditary Cancer in Clinical Practice 2010, 8(Suppl 1):O5

**Background/methods:** The CAPP2 Study evaluated 600mg enteric coated aspirin and/or 30gms of Novelose (resistant starch) in a double blind factorial RCT in 1071 carriers of Lynch syndrome over a treatment period of 1 to 4 years, mean 29 months.

**Results:** The trial, reported in December 2008 [1], showed that there was no difference between the treatment and placebo groups for new colorectal neoplasia. Follow-up data for 667 participants for up to 120 months (mean 51m) is now available. Analysis reveals a striking

reduction in subsequent cancers; overall, 102 participants have developed 110 Lynch syndrome cancers. Despite equal numbers being randomised to aspirin or placebo, cancer sufferers in the aspirin group are outnumbered 2 to 1. Lifetable analysis for time to first Lynch syndrome cancer reveals a hazard ratio of 0.62(0.41, 0.96)  $p=0.03$ . There is a clear effect of duration of treatment: <24months on treatment OR 0.90 (0.45, 1.81)  $p=0.78$ , treated >24 months OR 0.50 (0.28, 0.86)  $p=0.01$ .

**Conclusions:** All carriers of Lynch syndrome should consider aspirin chemoprevention. A dose finding study, CAPP3, is under development. It will compare different doses of aspirin over a 5 to 10 year period.

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#### Reference

1. Bum J, Bishop DT, Mecklin JP, et al.: Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch Syndrome. *NEJM* 2008, 359(24):2567-78.

#### O6

##### Effect of smoking on urothelial cancer risk in individuals with Lynch syndrome

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**Background:** Cigarette smoking is a well-described risk factor for a number of cancers and has been implicated as the most significant cause of urothelial cancer, conferring up to a 7-fold increased risk. Urothelial cancers are also part of the spectrum of cancers associated with Lynch syndrome. Several studies have looked at the impact of gene-environment interaction on cancer risk in Lynch syndrome and have found that smoking may increase the risk for colorectal cancer. However, the interaction of smoking and mismatch repair (MMR) genotype has never been evaluated for urothelial cancer risk.

**Methods:** Three existing cancer registry data sets are being utilized for this analysis including Colon-Cancer Family Registries, Dana-Farber Cancer Institute, and City of Hope. These data sets contain information about individuals with confirmed MMR gene mutations, age, race, gender, cancer diagnoses, and smoking status. Subjects were recruited using different strategies, with some being identified through population based recruitment and others being identified through high-risk clinics. Urothelial cancers included transitional cell cancers of the collecting system and bladder. Individual subject data will be assigned weights associated with inverse probability of being included in the sample based on recruiting methods and stratified to account for population versus clinic recruitment. A standardized incidence ratio (SIR) will be calculated by comparing the observed versus expected number of urothelial cancers among smokers and nonsmokers with MMR repair mutations. SEER data will be used to determine the expected number of cancers. Poisson regression techniques will be used to determine if smoking has a significant effect on the SIRs.

**Results:** From these three datasets, 1185 MMR mutation carriers were identified, and smoking data was available for 1107 (93.4%). Subjects were dichotomized as ever smokers if they had ever smoked a cigarette a day for three or more months or never smokers. Based on this definition 580 (52.4%) were never smokers, and 527 (47.6%) were smokers. There were a total of 34 urothelial cancers diagnosed in the entire study population, corresponding to a prevalence of 3.1 %. The mean age at diagnosis of urothelial cancer was 55.5 years (range 34-79 years). Urothelial cancer was the first cancer diagnosis in 10 cases (29.4%). Thirteen (38.2%) had one prior cancer, and 11(32.4%) had two or more prior cancers. Smoking data were available on 26 cases. Of those, 16 (61.5%) occurred in nonsmokers, and 10 (38.5%) occurred in smokers.

**Conclusion:** Our data suggest that the prevalence of urothelial cancer in MMR mutation carriers is approximately 3%. Risk estimates will be

adjusted for age and gender and appropriately weighted and stratified to account for subject ascertainment, in order to complete our calculation of the SIR. Determining the role of gene-environment interactions will be important for understanding differences in cancer risk among Lynch syndrome families and for targeting modifiable lifestyle factors for risk reduction.

**Acknowledgement:** We acknowledge the use of the Genetic Counseling and Biostatistics, and Survey Research Shared Resource which are supported by the Huntsman Cancer Foundation and an NCI Cancer Center Support Grant 5 P30 CA042014. The City of Hope hereditary cancer registry is supported in part by a General Clinical Research Center grant from NIH (MO1 RR00043) awarded to the City of Hope National Medical Center, Duarte, California.

#### O7

##### A predictive model of metachronous colorectal cancer occurrence in Lynch syndrome

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**Background:** Lynch Syndrome (LS) correlated colorectal carcinoma (CRC) patients show a tendency towards the development of multiple and metachronous lesions and, for this reason, a surgical prophylactic treatment, as total colectomy, is warranted. Considering the quality of life of patients treated with total colectomy, it is essential to determine risk factors of metachronous CRC. Aim of the study was to evaluate through a predictive model the patients that could really benefit from a surgical prevention.

**Methods:** We considered LS or suspected LS CRC patients enrolled by our Institutional Register of Hereditary Colorectal Tumors and submitted to a surgical resection of CRC, excluding those who had a total colectomy. Patients were characterized according to their genotype (MLH1, MSH2 and MSH6), sex and clinical features (age at diagnosis, tumour site, stage, grading, presence of colorectal adenomas and of extracolonic cancers) and were stratified in 4 mutually exclusive groups according to family characteristics: A) MMR gene mutation positive; B) Amsterdam criteria (ACI-II) positive, but mutation negative; C) AC-like and D) high risk. In order to identify a model for predicting metachronous CRC occurrence, for each patients' group a stepwise unconditional logistic regression model was fitted. All the regression equation included terms for gender, age in continuous as blocked terms. The predictive accuracy was assessed using the area under the receiver operating characteristics curve (AUC).

**Results:** A total of 1,604 CRC patients (M/F=1.02, 16.5% <40 yrs old) were considered (600 in group A, 117 B, 530 C and 357 D). During the follow-up, 181 developed metachronous CRC (11 %) and 354 (22%) an extracolonic cancer. The risks of metachronous CRC at 10 years were 21%, 16%, 16%, and 14% for group A, B, C and D, respectively. The predictive variables in the final model comprised for each group were: A) MLH1 mutation, the presence of colorectal adenomas and then occurrence of extracolonic cancers, B) occurrence of extracolonic cancers, C) high tumor grade and presence of colorectal adenomas. No significant predictors were identified for group D. AUC values, as a measure of discrimination of the various models, were 0.72, 0.78 and 0.76 for group A, B and C, respectively.

**Conclusions:** Metachronous CRC is a long-term moderate risk in LS patients. This suggests to recommend a prophylactic colectomy only to selected patients with well defined characteristics.

**Acknowledgement:** This study was supported by the Italian Association and Foundation for Cancer Research (AIRC).

## 08

### Linkage to chromosome 2q32.2-q35 in families with serrated neoplasia

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Hereditary Cancer in Clinical Practice 2010, 8(Suppl 1):08

**Background:** Causative genetic variants have to date been identified for only a small proportion of familial colorectal cancer (CRC). While conditions such as Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer, HNPCC) are caused by well defined genetic defects, the search for variants underlying the remainder of familial CRC is plagued by genetic heterogeneity. The recent identification of families with a heritable predisposition to malignancies arising through the serrated neoplasia pathway provides an opportunity to study a subset of familial CRC in which genetic heterogeneity may be greatly reduced.

**Methods:** A genome-wide linkage screen was performed on a large family displaying a dominantly inherited predisposition to serrated neoplasia genotyped using the Affymetrix GeneChip Human Mapping 10K Xba 142 Array, with parametric and nonparametric linkage analyses performed using Genehunter. Fine-mapping was undertaken in a further ten families using microsatellite markers spanning a 78 Nlb region of interest on chromosome 2, and parametric linkage scores and haplotypes generated using SimWalk. LOD scores were also generated under the assumption of locus heterogeneity (HLOD). Lynch syndrome was excluded in all families using mismatch repair gene (MMR) immunohistochemistry and somatic BRAF mutation testing. Coding and untranslated regions of five primary candidate genes were sequenced.

**Results:** Genome-wide linkage analysis revealed a region on chromosome 2 with overlapping parametric (maximum LOD score 1.6) and nonparametric (maximum NPL 4.3) peaks. Fine-mapping further localised the region to 2q32.2-q35, with a total LOD score of 1.1 and HLOD of 2.8, with 7 of 11 families showing evidence of linkage. Haplotypes segregating with affected status were present in all 7 families. No segregating variants were found in five primary candidate genes.

**Conclusions:** We have identified an approximately 12 Mb locus on chromosome 2q with linkage to familial CRC arising through the serrated neoplasia pathway. Up to 60% of serrated neoplasia families may be linked to the 2q locus, but a causative gene is yet to be identified.

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## POSTER PRESENTATIONS

### P1

#### Colorectal cancer risk in patients with inflammatory bowel disease and Lynch syndrome

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**Background:** Chronic inflammatory bowel disease (IBD) and Lynch syndrome (LS) are associated with an increased risk for developing colorectal cancer (CRC). After 8-10 years of pan-ulcerative colitis (DC), the risk of CRC is 2%, increasing by 0.5-1.0% annually. LS has been associated with a 60-80% lifetime risk of CRC. It is unclear whether individuals diagnosed with both IBD and LS would have a cumulative risk or earlier age of onset of CRC based on their diagnoses.

**Method:** Patients with IBD and a germline mismatch repair gene (MMR) mutation were identified through the Familial Gastrointestinal Cancer Registry at Mount Sinai Hospital in Toronto, Canada. Information on their IBD diagnosis, colorectal screening/surgery, medication use, family history and genetic test results were collected (Table 1).

**Results:** Five of 329 (1.5%) individuals with germline MMR mutations reported having a history of IBD.

**Conclusions:** Concurrent IBD and LS did not appear to predispose to early-onset CRC in our small case series.

### P2

#### Clinicopathologic and genetic features of young patients with colorectal cancer

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**Background:** Colorectal cancer (CRC) is the 3rd most common cancer in Canada, often occurring at older ages. While early-onset CRC can be suggestive of an inherited syndrome, the underlying genetic cause remains unexplained in many of these young individuals.

**Method:** Clinicopathologic features along with genetic and family information were collected on individuals diagnosed with CRC ≤35 years

Table 1 (abstract P1)

| Case #                                             | 1           | 2          | 3          | 4               | 5                 |      |
|----------------------------------------------------|-------------|------------|------------|-----------------|-------------------|------|
| Gender                                             | M           | F          | F          | M               | F                 |      |
| Ethnicity                                          | Caucasian   | Jewish     | Caucasian  | Caucasian       | Caucasian         |      |
| MMR Mutation                                       | MLH1        | MSH2       | MSH2       | MSH2            | MSH6              |      |
| Age of IBD dx                                      | 27          | 20         | 27         | 32              | 23                |      |
| Site of IBD                                        | Ileum       | Pancolitis | Pancolitis | Proctitis       | Pancolitis        |      |
| Colectomy, age                                     | 21          | 57         | 43         | 44              | 63                |      |
| Cancer/dysplasia                                   | CRC dx 21   | LGC*       | None       | TVA/HGD** dx 44 | Endometrial dx 57 |      |
| Smoking hx                                         | N           | Y          | N          | Y               | N                 |      |
| IBD medication                                     | 5-ASA       | N          | Y          | Y               | Y                 |      |
|                                                    | Steroids    | N          | Y          | Y               | N                 | Y    |
|                                                    | Antibiotics | N          | Y          | Y               | Y                 | N    |
| Age of CRC in 1 <sup>0</sup> or 2 <sup>0</sup> kin | # of kin    | 2          | 3          | 4               | 5                 |      |
|                                                    | Mean age    | 40.5       | 30.7       | 35.5            | 49.7              | 78.4 |

\*LGD – low-grade dysplasia on random screening biopsy

\*\*TVA/HGD – tubulovillous adenoma with foci of high-grade dysplasia

old identified through the Familial Gastrointestinal Cancer Registry in Toronto, Canada.

**Results:** 441 individuals from 353 families were identified, and to-date, medical records confirmed 254 diagnoses, which were included for analysis. Ninety patients (35.4%) had germline mutations in self or kin (31 *MSH2*, 36 *MLH1*, 1 *MSH6*, 3 *PMS2*, 24 *APC*, 2 *MYH* biallelic and 1 *BRCA2*). Individuals were classified into six categories; (a) 74 had Lynch syndrome (LS) confirmed by germline mutation or tumour deficiency (b) 4 had constitutional mismatch repair-deficiency (CMMR-D) (c) 61 had polyposis (mutation positive, >25 adenomas or hamartomatous polyps), (d) 6 met Family X criteria, (e) 7 had inflammatory bowel disease (IBD), and (f) 102 were unclassified (NOS), with 69 of these individuals having MSS and/or IHC intact tumours.

On average, patients with CMMR-D presented younger, with a mean age of 14 years old at diagnosis. 65.2% of patients with LS presented with a proximal tumour (65.2%) compared with the polyposis (10.2%) and NOS (34.4%) groups. In contrast, 83% of polyposis patients and 65.5% of NOS patients presented with distal colon or rectal cancers.

Family history was significant for the majority of LS patients with 54 of 73 (74%) meeting Amsterdam I or II criteria. Two of the 7 patients with IBD, and 15 of 98 NOS patients also met Amsterdam I/II criteria, as opposed to the CMMR-D families where none met these criteria. Six LS patients presented with sporadic CRC, as did approximately 25% of polyposis patients and 59.2% of the NOS patients.

**Conclusions:** Cancer site differs between individuals ≤35 years with LS, polyposis and NOS CRC. Greater than 1/3 of patients presented with no significant family history of CRC. While the majority of patients diagnosed with CRC ≤35 have a known hereditary CRC syndrome or risk predisposition, 69 of 221 (31.2%) of individuals appear to have no recognizable syndrome.

### P3

#### Heritable epigenetic mutation of MLH1 in a mother and daughter with Lynch syndrome

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**Background:** Lynch syndrome is a hereditary predisposition to colorectal and endometrial cancers, in addition to cancers of the stomach, ovary, upper urinary tract, small bowel, hepatobiliary tract, skin and brain. Lynch syndrome is caused by defects in DNA mismatch repair (MMR), and germline mutations in *MLH1*, *MSH2*, *MSH6* and *PMS2* as well as high levels of tumor microsatellite instability (MSI) and loss of MMR protein expression are frequently found. MMR deficiency due to loss of *MLH1* in tumor tissue may also be due to gene silencing resulting from hypermethylation of the *MLH1* promoter, which is found in 15% of sporadic colorectal and endometrial cancers, and as the second "hit" in some individuals with germline mutations in *MLH1*. Recently, epigenetic silencing of *MLH1* in normal body cells has been proposed as a novel cause of predisposition to Lynch syndrome associated tumors. Twenty five cases of hypermethylation of the *MLH1* promoter in peripheral blood (*MLH1* epimutation) of individuals with young onset colorectal cancer and/or endometrial cancer have been reported. The heritability of *MLH1* epimutation is still under investigation.

**Methods and results:** A 39-year-old woman from the Philippines was diagnosed with stage III rectal cancer. Her rectal biopsy was screened for evidence of MMR deficiency, which showed high levels of MSI and loss of *MLH1* and *PMS2* protein expression. Her mother was diagnosed with synchronous colon and endometrial cancers at age 40. She underwent germline mutation analysis of *MLH1* which failed to identify a mutation. Her rectal tumor was screened for *MLH1* promoter methylation and BRAF V600E, which showed hypermethylation of the *MLH1* promoter in both tumor and normal colonic mucosa, and negative BRAF V600E. Analysis of *MLH1* promoter methylation in her peripheral blood was consistent with *MLH1* epimutation. Tissue from her mother's colon tumor, endometrial

tumor, and normal body tissue showed high levels of MSI, loss of *MLH1* protein expression, negative BRAF V600E, and hypermethylation of the *MLH1* promoter. Her mother died from her colon cancer in 1995, thus peripheral blood was not available. The patient has two unaffected siblings, ages 31 and 35, who have undergone *MLH1* epimutation testing. Neither showed hypermethylation of the *MLH1* promoter in peripheral blood.

**Conclusions:** This case report represents only the third known instance of maternal, transmission of *MLH1* epimutation. The first was *MLH1* epimutation in an unaffected son of a woman with endometrial, colorectal, and rectal cancers who was found to have *MLH1* epimutation. The second was *MLH1* epimutation in the 64-year-old unaffected mother of a young woman with colorectal cancer at age 39 and *MLH1* epimutation. To our knowledge, our case is unique in that it represents the first case of *MLH1* epimutation in a clinically affected mother and daughter, supporting the heritability of *MLH1* epimutation as a rare but important cause of Lynch syndrome.

### P4

#### Intramucosal adenocarcinoma arising within a colonic polypoid ganglioneuroma in a 21 year old female with Cowden syndrome

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**Background:** Cowden syndrome (part of the PTEN Hamartoma Tumor Syndromes) is a relatively rare autosomal dominant genodermatosis which is characterized by the growth of lesions in multiple organ systems, including skin, breast, thyroid, endometrium and central nervous system. While most of these lesions are benign, Cowden syndrome confers a substantial risk for several cancers including breast, thyroid and endometrial cancer. Hamartomas of the colon are seen; while there are reports of colon cancer in patients with Cowden syndrome, specialized screening for colon cancer is typically not recommended (NCCN Practice Guidelines in Oncology, v.1.2009). Here, we report a rare case of a large adenoma with intramucosal adenocarcinoma associated with a colonic ganglioneuroma in a young woman with confirmed Cowden syndrome.

**Case:** A 21 year old female presented to our colorectal surgery department for a second opinion regarding indications for surgical colectomy. Past history was remarkable for a right hemicolectomy at age 6 for an obstructing right colonic mass. At age 14, she underwent a colonoscopy that revealed multiple polyps which were ganglioneuromas. At age 18, she underwent genetic evaluation for Cowden syndrome and was found to have a deleterious mutation in the *PTEN* gene, R130Q (CGA->CAA). Physical exam was remarkable for macrocephaly, papillomatosis of the tongue and oral mucosa and several large lipomas on her back. Available family history was negative for Cowden-related diagnoses. At age 20, she developed chronic crampy abdominal pain, diarrhea, rectal bleeding and iron-deficiency anemia. Colonoscopic examination revealed multiple polyps ranging in size from 0.3 to 1.2 cm, which were prolapsing and causing intermittent obstruction. Biopsies of several polyps revealed ganglioneuromas, as well as fragments of tubular adenoma. She underwent subtotal colectomy with ileorectal anastomosis and examination of the excised colon revealed ganglioneuromatous polyposis (>100 small polypoid ganglioneuromas with intramucosal ganglioneuromal proliferation in non-polypoid colonic mucosa) as well as four large (2.5-6 cm) ganglioneuromas. One of these large ganglioneuromas was associated with an adenoma with high-grade dysplasia and focal intramucosal adenocarcinoma. The patient did well after surgery, and the recommendation was made to continue endoscopic surveillance of the rectum every 6 months to screen for additional polyps.

**Conclusion:** Reports of malignant transformation of hamartomas are uncommon in Cowden syndrome. Interestingly, in one of the few reported cases of adenocarcinomas arising within hamartomas in Cowden syndrome, the position of the mutation (R130X) was the same as in this patient [1], indicating that there may be a genotype-phenotype correlation. This case illustrates the importance of endoscopic evaluation in Cowden patients with gastrointestinal complaints.

## Reference

1. Bosserhoff, et al.: Multiple colon carcinomas in a patient with Cowden syndrome. *Int J Mol Med* 2006, **18**(4):643-7.

## P5

### Lynch syndrome-chasing a better ascertainment rate in British Columbia

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**Background:** With a population of approximately 4.380 million people and an estimated Lynch syndrome mutation prevalence of 1/531, there are an expected 8000 individuals with Lynch syndrome in British Columbia. The Hereditary Cancer Program (HCP) of the BC Cancer Agency (BCCA) has provided clinical testing for Lynch syndrome since 2004 to patients across the province. Currently, there are approximately 100 patients with confirmed Lynch syndrome mutations in the BCCA database. Potential obstacles in ascertaining Lynch syndrome through a traditional clinic-based approach include physician awareness of referral criteria, patient's lack of knowledge of cancer family history, patient compliance, and availability of tumour tissue for testing. Given these obstacles, a population based approach to identifying Lynch syndrome through incident testing of newly diagnosed colorectal cancers under age 50 by microsatellite instability testing (MSI) was launched in BC in June of 2008.

**Methods:** Chart review of a cohort of patients referred for genetic counselling at the RCP during 2004-2006 and a cohort of consecutive colorectal cancer cases referred directly for MSI testing to the BCCA Genetics Laboratory (June 2008-June 2009). Mutation prevalence and clinicopathologic characteristics will be compared between the two groups. Clinical and demographic characteristics of the groups will also be compared to non-referred cases diagnosed under 50 in the province.

**Results:** Our previous clinic-based results showed a 14.3% prevalence of Lynch syndrome mutations among the index cases tested for whom results were available. 76% of tumour results were microsatellite stable and intact for MLH1 and MSH2 proteins. The sensitivity of the program's referral criteria was about 83.3% with an approximate confidence interval of 68.2%-96.8% and the positive predictive value was about 38.3% with an approximate confidence interval of 17.7%-60.0%. The prevalence of Lynch syndrome mutations dropped to 3.2% among all patients referred for genetic counseling. From July 2008 to July 2009, a total of 37 incident colorectal cases diagnosed under age 50 were referred directly to the BC Cancer Agency's cancer genetics lab. 73% were microsatellite stable while additional testing is underway on the 10 MSI high cases. Further comparisons between the groups will be presented.

**Conclusion:** Aside from becoming increasingly important for prognosis and predictive response to chemotherapy, population based MSI analysis on newly diagnosed colorectal cancer is expected to improve the rate of Lynch syndrome ascertainment in BC.

## P6

### Impact of mismatch repair (MMR) genetic test result on perceived cancer risk and cancer screening

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**Background:** Information recall after genetic testing has been examined extensively in patients at risk for Hereditary Breast Ovarian Cancer. We examined perceived cancer risk, screening practices, and genetic testing-specific distress in individuals undergoing genetic testing for Lynch syndrome.

**Methods:** Individuals who underwent clinical genetic testing for Lynch syndrome at Dana Farber Cancer Institute were enrolled in a longitudinal

questionnaire study eliciting information on perceived cancer risk, cancer worry, cancer screening and health behaviors prior to testing and after a clinical visit at which genetic test results were disclosed. Level of genetic test specific distress was assessed using the Multidimensional Impact of Cancer Risk Assessment Questionnaire (MICRA), and comparisons between groups were made using Kruskal Wallance non parametric analyses.

**Results:** 129 subjects (average age 47 years) completed questionnaires, 68% were female and 53% had a personal history of cancer. Genetic test results were classified as: Positive for pathogenic MMR mutation (n=23, 18%), True Negative for familial MMR mutation (n=17, 13%), Indeterminate negative (no previously identified family mutation) (n=79, 61%), and Variant of uncertain significance (VUS) (n=10, 8%). 116/129 (90%) of participants correctly recalled their genetic test result. When asked to estimate their cancer risk compared to other people their same age, 22/23 (96%) of individuals with a positive genetic test result correctly indicated that they were at higher risk, and 14/17 (82%) individuals with a true negative result indicated that their risk was the same as other people their age. However, 36/79 (46%) of those with indeterminate negative results incorrectly reported their cancer risk was now the same or lower compared with others their age. 111/129 (86%) of participants indicated that they worried about cancer the same or less than before they knew their genetic test result. Median genetic test-specific distress scores for individuals who received positive or VUS test results were significantly higher compared with indeterminate negative and true negative results (p < 0.001).

All individuals with a positive genetic test result reported that they planned to have colorectal cancer surveillance once a year or more frequently. Interestingly, 61/79 (77%) of individuals with indeterminate negative results and 7/17 (41%) of those with true negative tests still planned to undergo colonoscopy screening every 2 years or more frequently.

**Conclusions:** Overall, participants accurately recalled the result of their genetic test for MMR mutations. Although some individuals with indeterminate negative results may misinterpret their test result as meaning that their cancer risk is "lower," most plan to continue frequent colorectal cancer surveillance. While only 8% of our cohort received a VUS result, our findings suggest that these patients may experience genetic test-specific distress comparable to that of individuals who receive a positive genetic test result. Our results suggest that post test counseling is necessary to reinforce clinical implications of genetic test results and recommendations for cancer screening.

## P7

### Large serrated polyps: molecular and familial links to a serrated neoplasia predisposition

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**Background:** The serrated pathway to colorectal cancer is associated with a CpG-island methylator-phenotype (CIMP) and is distinct of the classical adenoma-to-carcinoma sequence. There is increasing evidence that a subset of hyperplastic polyps (HPs) serves as intermediates in an oncogenic sequence resulting in a CIMP colorectal cancer. This study analyzes molecular changes in large HPs to define their potential relationship to the serrated polyp pathway and links them to a predisposition to colorectal cancer.

**Methods:** Large serrated polyps (>20 mm) were identified by review of a colorectal polyp database and corresponding paraffin-embedded pathology specimens were retrieved. DNA was isolated from tissue blocks and methylation-specific quantitative real-time PCR analysis (MethyLight) was used to determine CIMP status (5 marker panel), methylation of mutated in colon cancer (MCC) gene, and the MLH1 gene. Polyp DNA was screened for mutations in the oncogenes KRAS and BRAF. Patient personal and family history of colorectal cancer was reviewed.

**Results:** Thirty-four large serrated polyps were studied. 28 were analyzed for BRAF of which 26 (93%) were mutant at V600E. 30 polyps were analyzed for CIMP, of which 18 (60%) were CIMP+. Of the 28 BRAF mutants, 20 had CIMP analysis done as well: 12/20 (60%) were CIMP+ and 8/20 (40%) were CIMP-. Of the 12 CIMP+, BRAF mutant polyps, 3 of 4 had methylated MCC but none of 4 had methylated MLH1. All polyps were KRAS wild type. 22 patients with large serrated polyps had an available personal and family history. Eight of 22 (36%) had a personal and 6 of 22 (27%) had a family history of colorectal cancer. Six of the eight (75%) with a personal history and 3 of the 6 (50%) with family history of colorectal cancer were CIMP+.

**Conclusions:** Large serrated polyps represent a subset of serrated lesions that appear to be initiated by BRAF mutations and progress toward cancer through subsequent methylation events. These polyps are associated with significant personal and familial history of colorectal neoplasia and likely represent part of a serrated neoplasia disposition.

## P8

### Hyperplastic polyposis syndrome: a call for broader diagnostic criteria

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**Background:** Hyperplastic Polyposis Syndrome (HPS) is a rare disease characterized by multiple or large hyperplastic polyps and carries an approximately 40% lifetime colorectal cancer risk. Although a genetic basis has not been established, HPS is believed to be a heritable syndrome and is diagnosed by clinical criteria as set forth by the World Health Organization (WHO). Based on clinical experience, we hypothesized that WHO criteria may be narrowly restrictive and misses some patients with an increased malignancy risk.

**Methods:** For this study, HPS was defined by meeting at least one of the following criteria: 1)  $\geq 20$  HPs anywhere in the colon, 2)  $\geq 5$  HPs proximal to the sigmoid colon, 3)  $\geq 2$  HPs at least 10mm in size, 4) any HPs and a 1st degree relative with HPS. Colonoscopy and pathology databases were retrospectively reviewed for patients meeting criteria. Patient

demographics, colonoscopic findings, and personal and family history of cancer were recorded.

**Results:** Sixty patients (38 males, 22 females) meeting at least one of the above criteria were included. Only 19 of these 60 patients (32%) also satisfied WHO criteria for HPS. Results are summarized in Table 1. Importantly, of the additional 41 patients only meeting the broader criteria, 27% had a personal history and 44% had family history of colorectal cancer. This group also had extracolonic malignancies including breast, lung, prostate, and testicular cancer.

**Conclusion:** HPS is associated with a personal and familial risk of colorectal cancer and other malignancies. Applying broader definitions identifies an additional population of patients with increased personal and familial cancer risk. More inclusive criteria should be used until a genetic basis of disease better defines cancer risk.

## P9

### Changing causes of death in Familial Adenomatous Polyposis:

#### 20 years of progress

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**Background:** Patients with FAP are at risk of dying from multiple benign and malignant tumors, from surgical complications, and comorbid diseases. We previously evaluated and published causes of death in FAP patients in 1990. This study analyzes patterns of mortality in the ensuing 2 decades and compares the two time periods to determine if advances in medicine and technology have changed clinical outcomes.

**Methods:** Causes of death were extracted from the 1990 study via the manuscript. Causes of death since then were determined from the registry database and confirmed by chart review.

**Results:** In 1990 there were 178 FAP families in the registry. Currently, 761 families are enrolled in the registry. The mean age of patients in the registry before 1990 was 36.5 and the mean age since then is 54.5. There is a significant increase in life expectancy in patients after 1990. 212 patients have died (0.28 deaths per family); 110 before 1990 (0.62 deaths per family) and 102 since (0.17 deaths per family). Causes of death are listed in Table 1.

"Other" deaths include cancers of the thyroid, stomach, esophagus, pancreas, breast, ovary and lung. There were also 2 suicides and one death from pancreatitis. Overall there have been fewer deaths per family since 1990. Deaths from colorectal and periampullary/duodenal cancer have declined (even if the "unknown" category is excluded) while those for desmoid remain constant. Perioperative deaths are fewer.

**Conclusion:** Although the main causes of death in FAP remain the same, improvements in education and in access to screening and surgical techniques have decreased the overall mortality rates. Continued improvements in all aspects of patient care could further improve patient outcomes in FAP.

**Table 1 (abstract P8)**

| HPS Criteria      | N  | Colorectal Cancer History |          | Other Cancer History |          |
|-------------------|----|---------------------------|----------|----------------------|----------|
|                   |    | Personal                  | Family   | Personal             | Family   |
| WHO               | 19 | 5 (26%)                   | 4 (21%)  | 8 (42%)              | 7 (37%)  |
| Only New Criteria | 41 | 11 (27%)                  | 18 (44%) | 9 (22%)              | 11 (29%) |
| All Patients      | 60 | 16 (27%)                  | 18 (37%) | 12 (23%)             | 18 (30%) |

**Table 1 (abstract P9)**

| Cause of death                      | Before 1990 | Age at death | Since 1990 | Age at death |
|-------------------------------------|-------------|--------------|------------|--------------|
| Colorectal cancer                   | 64 (58.2%)  | 41.1         | 41 (40.2%) | 49.4         |
| Desmoid disease                     | 12 (10.9%)  | 33.8         | 9 (8.8%)   | 34.6         |
| Periampullary cancer                | 9 (8.2%)    | 49.1         | 4 (3.9%)   | 51.7         |
| Brain cancer                        | 8 (7.3%)    | 19.6         | 2 (2%)     | 81           |
| Perioperative                       | 5 (4.5%)    | 32.6         | 3 (2.9%)   | 59.5         |
| Accident                            | 3 (2.7%)    | 31.3         | 0          | 0            |
| Other                               | 9 (8.2%)    | 38.4         | 24 (23.5%) | 53           |
| Unknown                             | 0           | 0            | 19 (18.6%) | 57.8         |
| Overall cancer (excluding desmoids) | 85 (77.3%)  |              | 57 (55.9%) |              |

## P10

### High risk clinic for hereditary colorectal neoplasia: a focus for patient care and an opportunity for clinical research

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**Background:** Patients with hereditary colorectal neoplasia and their families need specialized care to plan for appropriate surveillance and to ensure that they receive the most favorable treatment. This involves coordinating multidisciplinary appointments on the same day to minimize inconvenience to patients. We have established a special high risk clinic for these patients and their families. In this study we are reporting our activity for the last 5 years.

**Methods:** Initially the clinic ran one morning a month but has grown in the last 2 years adding another half day session. Requests for appointments were triaged by registry coordinators. Patients with syndromes of hereditary colorectal neoplasia were eligible for this clinic if the necessary appointments included multiple physicians. The clinic is staffed by one of three colorectal surgeons, one gastroenterologist, one genetic counselor, one hepatobiliary/upper GI surgeon and often by a clinical geneticist.

**Results:** From January 2004 to November 2008 there have been 440 patient visits (Table 1), 68 colonoscopies, 180 flexible sigmoidoscopies, and 226 EGDs (Table 2), 44 consults to medical genetics were performed, and 9 to general surgery (Table 3). Clinic activity generated 101 surgeries including 37 colectomies and 7 duodenectomies. If all the appointments were done separately this would mean at least 967 separate visits.

**Conclusion:** The High Risk Clinic is a valuable resource for patients, insurers, and registry workers.

**Table 1 (abstract P10)**

| Patients seen by syndrome | 2004      | 2005      | 2006      | 2007       | 2008       |
|---------------------------|-----------|-----------|-----------|------------|------------|
| FAP                       | 41        | 63        | 85        | 92         | 101        |
| MYH                       | 0         | 1         | 3         | 1          | 2          |
| JPS                       | 5         | 4         | 0         | 3          | 5          |
| PJS                       | 1         | 0         | 1         | 0          | 0          |
| HPS                       | 0         | 0         | 1         | 1          | 4          |
| HNPCC                     | 0         | 0         | 4         | 6          | 2          |
| Other                     | 2         | 5         | 2         | 1          | 4          |
| <b>Total</b>              | <b>49</b> | <b>73</b> | <b>96</b> | <b>104</b> | <b>118</b> |

**Table 2 (abstract P10)**

| Procedures    | 2004 | 2005 | 2006 | 2007 | 2008 |
|---------------|------|------|------|------|------|
| C-scope       | 9    | 11   | 24   | 12   | 12   |
| UGI           | 26   | 46   | 41   | 45   | 48   |
| Capsule       | 0    | 2    | 1    | 0    | 2    |
| Sigmoidoscopy | 13   | 40   | 45   | 49   | 43   |
| Surgery       | 5    | 8    | 16   | 31   | 41   |

**Table 3 (abstract P10)**

| Referrals        | 2004 | 2005 | 2006 | 2007 | 2008 |
|------------------|------|------|------|------|------|
| Medical Genetics | 4    | 11   | 1    | 20   | 18   |
| Thyroid Consult  | 0    | 0    | 0    | 0    | 4    |
| General Surgery  | 2    | 2    | 5    | 0    | 0    |

## P11

### Evolution of a High-Risk Cancer Registry: past, present and future

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**Background:** Huntsman Cancer Institute's High-Risk Cancer Clinics at the University of Utah has followed high-risk colon, pancreatic, melanoma and breast cancer patients, under the auspices of independently run and funded registries, for over 15 years. As knowledge of the genetics of high-risk syndromes and cancers has grown, awareness has emerged of the clinical overlap between risks for these conditions, previously viewed as distinct. To address this growing understanding and to assist in the facilitation of broad-based research efforts, we have embarked on a plan to combine these registries into one single global high-risk cancer registry.

**Methods:** The previously independent high-risk colon cancer (~1,100 enrolled; > 1,300 blood and tissue samples) and pancreatic cancer (242 enrolled; > 195 blood samples) registries were merged into a single IRB-approved Hereditary Gastrointestinal Cancer Registry (HGCR). This merging of registries will take advantage of the known clinical and genetic overlap between these two populations. Research records of participants automatically rolled over into the new registry, therefore re-enrollment was not mandatory. The combined registry enrolls individuals and their family members with a personal and/or family history of gastrointestinal cancer (GI) syndromes and conditions, including those of the pancreas, stomach, and colon as well as large kindreds with excess cancers and unknown etiologies.

**Results:** The combined HGCR currently includes over 1,400 enrolled participants from ~400 kindreds. Over 1,500 DNA, cell lines, serum and tissue samples are available for affiliated investigator use. Enrolled participants complete personal, family and medical history questionnaires and medical record releases and are asked to provide blood/buccal and surgical tissue samples (where applicable). The HGCR supports multiple types of basic and translational research projects, including two chemoprevention trials for Peutz-Jeghers patients (ongoing) and FAP patients (pending), psychosocial assessments in high-risk cancer families, and multiple molecular studies for mutation identification methods. Family expansion efforts are focused on expanding populations eligible for registry-supported studies. Substantial progress has been made in collecting and abstracting medical records of cancers and GI procedures. More than 800 medical record procedures, including available genetic test results, have been abstracted since the launch of the new registry. Increases in participant referrals to and from genetic counselors, health-care providers and eligible research studies (internally and externally) have been noted and are expected to increase considerably over time.

**Conclusions:** Since the successful amalgamation of the colon and pancreatic registries into a single registry, we recognize the necessity and feasibility for combining additional high-risk registries into a large global cancer registry. Future plans include integrating with our high-risk melanoma and breast cancer registries.

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## P12

### Do precursor polyp burdens help distinguish Lynch versus non-Lynch microsatellite unstable colorectal cancers?

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**Background:** Microsatellite instability (MSI) within colorectal cancers (CRC) may develop through inherited germline mutations in mismatch

repair (MMR) genes (Lynch Syndrome) or sporadic epigenetic methylation of tumor suppressor or repair genes (methylator pathway). Although the molecular mechanisms in each pathway have been described, their associated precursor polyp burdens are not well-defined. This study analyzes precursor polyp burdens occurring within patients with MSI-H colorectal cancers associated with Lynch Syndrome (LS) or those with a methylator pathway cancer phenotype.

**Methods:** MSI-H CRCs were identified either from an inherited CRC registry or clinic-based frozen tissue bank. Patients with confirmed MMR germline defects were defined as LS. MSI-H tumors considered to be methylators were defined by previously determined CpG island methylator phenotype (CIMP). These two groups were also compared to MSS/CIMP-negative tumor controls. Corresponding patient demographics, all prior preoperative colonoscopy, operative, and pathology reports for polyp characteristics were reviewed.

**Results:** 114 patients were included: 29 LS, 22 Methylator, and 63 MSS/CIMP-negative. No differences were observed between groups in terms of gender, total number or percentage of patients with polyps, and polyp location. The LS group was younger, had larger polyps size (1.0 cm vs. methylators, 0.4 cm,  $p=0.02$ ), and more malignant polyps (4/30 vs. methylators (0/26) and MSS/CIMP-N (1/100),  $p=0.01$ ). Although adenomas were the most prevalent polyp type in all groups, serrated polyps were located more frequently in the right colon in methylators (9 of 12) compared to LS patients (1 of 5),  $p=0.01$ . Importantly, the percentage of serrated polyps varied by group with 46% (12/26) incidence in methylators compared to 17% (5/30) in LS ( $p=0.02$ ) and 24% (24/100) in MSS/CIMP-negative patients ( $p=0.03$ ).

**Conclusions:** Polyp burdens associated with MSI-H CRC vary depending on the etiology of microsatellite instability. While LS patients tend to develop adenomas similar to the general population, an increased relative burden of serrated polyps is associated with the methylator phenotype. These findings may help guide investigation into suspected Lynch syndrome.

### P13

#### Differential gene expression in primary colonic tissue from control, FAP and AFAP patients reveals unique signatures with diagnostic potential

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**Background:** Familial adenomatous polyposis (FAP) is a colon cancer syndrome with a prevalence of 1:10,000. Patients have 100's to 1000's of precancerous colonic polyps and nearly 100% risk of developing colon cancer at an average age of 39 years in the absence of colon surveillance and surgery. Mutations in the APC gene lead to FAP as well as an attenuated form (AFAP) which presents with variable phenotypic expression, reduced polyp numbers and reduced cancer risk as compared to FAP. Current methods for the clinical diagnosis of genetic diseases most commonly involve analysis of germline DNA. Germline DNA-based diagnosis can be incomplete, for example no mutation is found in approximately 20% of FAP and 50% of AFAP patients. The objective of this study is to determine a molecular profile of the colonic epithelia from patients with APC mutations leading to FAP or AFAP then to use this information to establish a gene expression signature for diagnosis and for better understanding of the disease in the primary affected tissue.

**Methods:** Fresh normal-appearing colonic epithelia were obtained as biopsies during endoscopy and immediately placed in RNA-later, a tissue preservative for RNA integrity. RNA was extracted using Qiagen RNeasy purification system. Agilent 44K RNA microarrays were run using mRNA from FAP patients ( $n=6$ ), AFAP patients ( $n=14$ ) and control patients ( $n=12$ ). Normalized log ratios for each sample vs. reference RNA were the input for analysis using the Rank Product to generate a p-value for significance of differential expression and to cluster using Ward's Method in the Spotfire DecisionSite software.

**Results:** Analysis using the Rank Product method found 48 mRNA probes with statistical significance ( $p<0.001$ ) that consistently distinguish between control, FAP and AFAP normal appearing colonic tissue. These probes are up in FAP vs. control but low in AFAP vs. control or vice versa and will be tested for their accuracy to classify FAP and AFAP patients. Differential expression was also evaluated to better understand the phenotypic variability within AFAP using 5 individuals with > 100 adenomas versus 6 individuals with < 20 adenomas with the identical APC mutation. Differential expression identified 245 probes with a p-value of <0.05. The most striking were DEFA5 and DEFA6, encoding microbicidal defensins involved in host defense, which consistently showed increased expression in the >100 adenoma group. It is not clear if this reflects a host or an environmental difference and will require further study.

**Conclusions:** In conclusion, a distinct gene expression signature can be identified in FAP vs. AFAP patients that, in turn, can be applied to diagnostics. A separate set of genes can also distinguish colonic phenotypic classes of individuals with the identical APC mutation and may suggest secondary factors that modify the phenotypic penetrance in AFAP.

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### P14

#### Audiology and Familial Adenomatous Polyposis: do you hear what I hear?

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Hereditary Cancer in Clinical Practice 2010, 8(Suppl 1):P14

**Background:** The APC protein has an important role in maintaining function of microtubules in the ear which plays a significant part in the mechanism of hearing. Preliminary data suggests that the APC protein is associated with an increased incidence of abnormal hearing which may affect intellectual function. We sought to assess the hearing among patients with FAP (Familial Adenomatous Polyposis).

**Methods:** Patients with FAP were recruited for an IRB (Institutional Review Board) approved study assessing hearing and intelligence. Hearing was tested by pure tone air conduction audiometry, less than or equal to 30 db at 3/4 of the following frequencies (500 Hz, 1000 Hz, 2000 Hz and 4000 Hz). Subjects were then administered the Kaufman Brief Intelligence Test (KBIT-2). We then analyzed the proportion of individuals with an abnormal audiometry as compared to age and gender adjusted normalized hearing standards.

**Results:** 44 patients were recruited from 42 families. Subjects included 22 men with a mean age of 42 years. When compared to normalized hearing standards, 19 (43.2%) of the 44 patients failed to meet the standard normal range. Audiologic abnormalities showed unilateral hearing impairment was documented in 6 patients, bilateral impairment in 13. Of these patients 63% were impaired at a single frequency; the other 37% were at multiple frequencies. 59% of patients showed right hearing impairment with the highest deficit (35%) at 2000 Hz. 71% of patients had left sided impairment with the greatest number (32%) at 4000 Hz.

**Conclusion:** A large subset of our sample of FAP patients (43.2%) had abnormal audiologic results when compared to the normalized standard. Differences in IQ scores for patients with and without audiologic abnormalities are not statistically significant, suggesting that these results do not reflect an association between hearing and intellectual functioning in our sample.

## P15

### Cognitive function in Familial Adenomatous Polyposis: anyone out there listening?

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**Background:** Preliminary data suggests the APC protein is critical for dependent pathways in the cochlea and may be important in cognition. Abnormal audiometries have been documented in Familial Adenomatous Polyposis (FAP). We studied cognitive function among patients with FAP.

**Methods:** FAP patients were recruited for an IRB (Institutional Review Board) approved study assessing intelligence using the Kaufman Brief Intelligence Test (KBIT-2), which provides Verbal, Nonverbal and Composite IQs. The KBIT-2 was administered and scored by individuals experienced in administration of psychometric measures. Mean scores were analyzed and compared to standard normal ranges.

**Results:** 44 subjects from 42 families (22 men), mean age of 42 years were included. KBIT-2 Composite IQ score was  $98.4 \pm 12.4$ , (95% CI (confidence interval) 94.5-102.3) which is within the average range of 90-109. 27 % of patients scored below average (less than 90) and 15% scored above average (greater than 109), not a significant imbalance (sign test  $p=0.33$ ). Nonverbal IQ scores show no difference from average, mean=100.5; 24% scored below and 27% scored above average. Verbal scores were  $95.5 \pm 12.0$  (95% CI 91.7 -99.2) significantly lower than average (one-sample T-test  $p=0.020$ ). There is an imbalance among patients with 27% below and 7% above the average range and a tendency toward lower than average scores (sign test  $P=0.06$ ). The mean number of points by which Nonverbal IQ exceeded Verbal IQ was  $5.0 \pm 12.5$  (95% CI 1.1 -9.0), (one-sample T-test  $p=0.013$ ). The non-verbal score exceeded the verbal score for 27 patients (65.9%), while the verbal score was larger for only 10 patients (24.4%) (Sign test  $p=0.008$ ).

**Conclusion:** Composite IQ scores suggest that FAP patients do not have lower IQ from the general population. However the verbal scores of FAP patients which are dependent on hearing are significantly lower than average and may reflect abnormal audiometries or other effects of the APC mutation on cognitive function.

## P16

### Genome wide association identified colorectal cancer susceptibility loci and colorectal cancer risk in Lynch syndrome

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**Background:** Recent genome-wide association studies (GWAS) have identified several common low-risk variants for colorectal cancer. Although some of the GWAS were enriched for young onset and family history positive colorectal cancer cases, it is not clear if these variants modify colorectal cancer risk for people with Lynch syndrome. In a case- unaffected sibling analysis of population and clinic based sibships, a study by Poynter *et al.* (2007) found a stronger association for risk variants in the 8q24 region (rs10505477 and rs6983627) with microsatellite instability (MSI)-high tumors. MSI-high tumors are characteristic of Lynch syndrome. Therefore we hypothesize that these variants may also influence colorectal cancer risk in Lynch syndrome. Recently Wijnen *et al.* (2009) have reported on some of the GWAS risk variants in Dutch Lynch syndrome families and although they did not

find an association between rs6983627 and colorectal cancer risk, other risk variants in 8q24 and 9p24 have yet to be characterized in Lynch syndrome.

**Methods:** In a retrospective cohort study design we analyzed 267 Lynch syndrome subjects from the M. D. Anderson Lynch syndrome registry with a proven DNA mismatch repair gene mutation. We genotyped 3 risk variants: 8q24 (rs10505477: T>C and rs6983627: T>G) and 9p24 (rs719725: A>C) and used Cox proportional hazards regression (Hazard ratios and 95% confidence intervals) to analyze the association between each of the risk variants and colorectal cancer risk while adjusting for sex and familial correlation.

**Results:** Of the 267 subjects from 120 families with 11767 person years of follow-up, 138 had colorectal cancer and the remaining was unaffected. We modeled each of the 3 variants as codominant, additive and recessive but none of them were associated with colorectal cancer risk in our cohort.

**Conclusion:** Although the GWAS identified colorectal cancer risk variants are potential modifiers of colorectal cancer risk in Lynch syndrome, it is possible that the lack of association seen in our data is due to our study being underpowered to detect the modest association typically associated with these common variants. Further studies with a larger sample size are warranted to confirm presence or true lack of an association.

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## P17

### An unusual tumor spectrum in Lynch syndrome caused by MSH6 mutation

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**Background:** Inherited cancer syndromes associated with acoustic neuroma (i.e. neurofibromatosis 2-NF2), pheochromocytoma (i.e. Von Hippel Lindau, NF1, multiple endocrine neoplasia syndromes, and hereditary paraganglioma syndrome), and colon cancer are well known. Lynch syndrome is the most common hereditary colon cancer syndrome and is caused by DNA mismatch repair dysfunction secondary to inherited mutations in one of MLH1, MSH2, MSH6, and less commonly PMS2. An increased risk for a variety of cancers is seen in patients with Lynch syndrome with the greatest risks being for colon and endometrial cancer. We report a Dutch patient with a history of bilateral acoustic neuromas diagnosed at 47, and pheochromocytoma and endometrial adenocarcinoma diagnosed at age 54. She had no family history or other signs/symptoms of NF2. Family history was significant for her brother having metachronous colon cancers at 42 and 51, and a maternal uncle having colon cancer in his 40s. The family does not fulfill either Amsterdam I or II criteria.

**Methods:** Clinical investigations for hereditary cancer predisposition were undertaken in our patient given her history of multiple primary tumors. Immunohistochemistry (IHC) for MLH1, MSH2, and MSH6 proteins, and genetic testing for Lynch syndrome were completed. In light of the history of bilateral acoustic neuromas, genetic testing for NF2 was also undertaken.

**Results:** Genetic testing for NF2 did not detect a mutation or deletion in the NF2 gene. IHC on tissue from the patient's endometrial adenocarcinoma and pheochromocytoma showed absent expression of MSH6. A pathogenic germline mutation in MSH6 (c.651\_652insT) was identified.

**Conclusions:** We report a potential new association of Lynch syndrome with pheochromocytoma and acoustic neuromas in a woman with Lynch syndrome caused by an MSH6 mutation. In this case, a diagnosis of Lynch syndrome was suspected due the history of endometrial adenocarcinoma in our patient and her family history of early colon cancer. Identification of a Dutch founder mutation in MSH6 confirmed the diagnosis. The absence of MSH6 expression by IHC in both the endometrial carcinoma and the pheochromocytoma highly suggests an association of the

pheochromocytoma with defective mismatch repair function secondary to the MSH6 mutation. Unfortunately, tumor studies could not be completed on tissue from the acoustic neuroma so it is difficult to say whether they arose independently or were also related to the diagnosis of Lynch syndrome. In this case, normal NF2 genetic testing and the absence of a family history of NF2 may suggest an association of acoustic neuromas with Lynch syndrome.

is the lack of males presenting with polyposis and the apparent overrepresentation of de novo mutations. Both of these observations may disappear as cohort size increases. However, there are other factors such as reduced access to regular and diagnostic medical services in other countries, communication barriers within families, and cultural and gender differences that might be at play.

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## P18

### Familial Adenomatous Polyposis (FAP) in 9 Hispanic women

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**Background:** Familial adenomatous polyposis (FAP) is a rare hereditary colorectal cancer syndrome estimated to account for about 1% of colorectal cancers. While there is variation in the FAP phenotype amongst individuals and families with mutations, it is characterized by a striking phenotype of colonic polyposis and other distinctive features such as desmoids and gastric fundic gland polyps. It is estimated that about 30% of APC mutations are de novo. APC mutations have been reported worldwide across different ethnic and racial groups. We report on the features of FAP seen in 9 Hispanic women with colonic polyposis, identified over 18 months.

**Methods:** Individuals were referred for cancer risk assessment. Genetic analysis of the APC gene, including sequencing and rearrangement studies, was conducted after counseling and informed consent.

**Results:** All of the individuals referred were women; the majority was originally from Mexico (67%) with the remainder from Central America. The average age at identification of polyposis was 37.2 years and 5 had concomitant colorectal cancer (average age 34.2 years). The most common site of cancer was the rectum and the most common extra-colonic finding was gastric polyps. The majority of women reported either no family history or cancer history inconsistent with FAP, suggesting de novo mutations. All individuals, for whom results are available, were found to have APC gene mutations. Results are found in Table 1.

**Conclusions:** These Hispanic women with FAP demonstrate a phenotype consistent with the existing understanding of this syndrome. Of interest,

## P19

### Characteristics of Lynch syndrome in 13 Hispanic Families

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Hereditary Cancer in Clinical Practice 2010, 8(Suppl 1):P19

**Background:** While the incidence of colorectal cancer is lower in Hispanics than in non-Hispanic Caucasians, it is the second most common cancer in this diverse ethnic population. Emerging data indicate hereditary colon cancer syndromes contribute to cancer burden regardless of race and ethnicity. These data derive from research and cohorts where Hispanics are underrepresented. Here we report on 14 individuals from 13 Hispanic families with Lynch syndrome.

**Methods:** After referral for cancer risk assessment, immunohistochemical staining was performed for the four MMR gene products and/or analysis of the appropriate gene(s) was initiated.

**Results:** Clinical features of the 14 individuals identified with Lynch syndrome are detailed below (Table 1). Of the 13 families, 9 (71 %) are from Mexico, 4 from Central America. Seventy-two percent presented first with colon cancer (64% right-sided); 14% presented first with gastric cancer; and 1 individual with uterine cancer. The average age at first cancer diagnosis was 38.6 years; 38.5 years for colon cancer. One third had two primaries, 3 synchronous. Five of the 13 families met Amsterdam I or II criteria, while 8 met Bethesda guidelines. Two were single-case indicators, two had multiple family members affected in only one generation, and the remainder had contributory family history but too distant to meet Amsterdam. Twelve individuals underwent genetic testing; 8 MLH1 mutations and 3 MSH2 mutations were detected. Pathology was thoroughly reviewed in 11 colon tumors; 2 were well differentiated, 6 were well to moderately differentiated and 3 were focally poorly differentiated,

**Table 1 (abstract P18)**

| Country of Origin* | Diagnosis                             |     | Polyps               | Extra-colonic Findings                | Family History**                                     | Gene Analysis |      |
|--------------------|---------------------------------------|-----|----------------------|---------------------------------------|------------------------------------------------------|---------------|------|
|                    | Cancer                                | Age |                      |                                       |                                                      |               | exon |
| MX                 | Cholangio                             | 48  | >100                 | gastric polyp                         | mom-co-44, sis-co-32+pan-64, sis-co-38, cousin-co-38 | Q1062X        | 15   |
| MX                 | Rectal                                | 35  | >100                 |                                       | sis-co-50                                            | IVS3-1G>A     |      |
| MX                 | Rectal                                | 35  | >100                 | 2 mesenteric desmoids; gastric polyps | mom died at 54 of a "tumor between heart & lungs"    | 3709delCA     | 15   |
| GU                 | None                                  | 39  | >100                 |                                       | maun-co mass, not ca-49                              | del exon 6-15 |      |
| MX                 | Rectal                                | 26  | Polyposis, # unknown | abdominal desmoid; 2 pilomatixomas    | mom-ut-45, mgm-GI ca-75                              | 3927del5      | 15   |
| HO                 | Sigmoid descending colon              | 42  | >100                 | gastric polyps                        | mgm-ut-35                                            | E268X         | 7    |
| MX                 | Rectal                                | 33  | >100                 |                                       | pun-"some polyps"                                    | 3183del5      | 15   |
| HO                 | Tubular adenoma high-grade dysplasia+ | 42  | >100                 | gastric polyps; duodenal polyps       | maun-br-20                                           | pending       |      |
| MX                 | None                                  | 35  | >100                 | gastric polyps; duodenal polyp        | none                                                 | pending       |      |

\*MX=Mexico; HO=Honduras; GU=Guatemala; +Surgery pending

\*\*sis=sister; co=colon cancer; pan=pancreatic cancer; ut=uterine cancer; br=breast cancer; maun=maternal aunt; pun=paternal uncle; mgm=maternal grandmother; GI=gastrointestinal (not otherwise specified)

**Table 1 (abstract P19)**

| Country of Origin** |    | 1 <sup>st</sup> Cancer Diagnosis |     | 2 <sup>nd</sup> Cancer Diagnosis |     | Family History Classification | IHC-Proteins unexpressed | Gene Analysis              |                |
|---------------------|----|----------------------------------|-----|----------------------------------|-----|-------------------------------|--------------------------|----------------------------|----------------|
|                     |    |                                  | Age |                                  | Age |                               |                          |                            | Gene           |
| 1                   | ES | Cecal                            | 37  | Transverse                       | 37  | Amsterdam I                   | hMLH1/hPMS2              | MLH1                       | S698X          |
| 2                   | GU | Sigmoid                          | 34  |                                  |     | Amsterdam I                   | hMSH2/hMSH6              | MSH2                       | S142X          |
| 3                   | MX | Sigmoid                          | 33  |                                  |     | Amsterdam I                   |                          | MLH1                       | 1105insT+      |
| 4                   | MX | Gastric                          | 31  | Rectal                           | 32  | Amsterdam I                   |                          | MLH1                       | R226X          |
| 5                   | MX | Uterine                          | 48  |                                  |     | Amsterdam II                  | hMLH1/hPMS2              | MLH1                       | Q409X          |
| 6                   | MX | Cecal                            | 47  | Descendng                        | 47  | Bethesda                      | hMLH1/hPMS2              | Declined                   |                |
| 7                   | GU | Cecal                            | 45  |                                  |     | Bethesda                      | hMLH1/hPMS2              | MLH1                       | ICS3-2A>G+     |
| 8                   | MX | Sigmoid                          | 40  |                                  |     | Bethesda                      | hMHS2/hMSH6              | None detected <sup>1</sup> |                |
| 9                   | MX | Cecal                            | 36  |                                  |     | Bethesda                      | hMSH2/hMSH6              | MSH2                       | Q593X          |
| 10                  | ES | Cecal                            | 31  |                                  |     | Bethesda                      | hMLH1/hPMS2              | MLH1                       | K618del        |
| 11                  | MX | Transverse                       | 45  | RCC-clear cell                   | 45  | Bethesda                      | hMLH1/hPMS2              | MLH1                       | del exon 2-3   |
| 12                  | MX | Splenic Flexure                  | 32  |                                  |     | Bethesda                      | Pending                  | MSH2                       | 2179delCinsAG+ |
| 13*                 | MX | Cecal                            | 44  |                                  |     | Bethesda                      | hMSH2/hMSH6              | MSH2                       | Q76X           |
| 14*                 | MX | Gastric                          | 37  | Cecal                            | 47  | Bethesda                      | hMSH2/hMSH6              | Declined                   |                |

\*Individuals 13 and 14 are brothers; \*\*MX=Mexico; ES=El Salvador; GU=Guatemala

<sup>1</sup>MLH1 and MSH6 sequencing (MSH6 VUS 4071ins4), MSH2/MLH1 rearrangement studies

+not reported in Leiden Variation Open Database or the Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff

3 exhibited tumor infiltrating lymphocytes, 3 showed Crohn's reaction, 9 demonstrated pushing borders, 3 contained dirty necrosis, and 4 were mucinous carcinoma (>50%) with an additional 4 cases showing mucinous features (<50%).

**Conclusions:** As the U.S. Hispanic population grows and access to cancer genetics services increases, the contribution of Lynch syndrome must be understood. In our cohort of Hispanic families, the early-onset right-sided colon cancer is consistent with known Lynch syndrome features. Of interest are the young age at diagnosis and the high number of families meeting only Bethesda criteria. Another area to explore is the frequency of gastric cancer in Hispanic families with Lynch syndrome, given the higher incidence of gastric cancer in Latin America.

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## P20

### A Familial Adenomatous Polyposis (FAP) patient education conference and its impact on patients and families

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**Background:** Individuals with familial adenomatous polyposis (FAP) require increased lifelong surveillance due to the high risk of colorectal cancer and extracolonic features. Despite the existence of well-established surveillance guidelines, studies have shown that lack of patient knowledge is a major hurdle to adherence. Patient education conferences represent an avenue for patients to obtain disease-specific information directly from experts. There is a paucity of data addressing the educational needs and characteristics of individuals who attend such conferences and the impact on their FAP-related knowledge.

**Methods:** Individuals with FAP identified through the institution's FAP registry and their family members were invited to attend an educational conference. Adult attendees were provided IRB approved baseline and follow-up surveys as part of their conference packets. The paired surveys were matched through the use of a unique survey identifier and contained items pertaining to demographic and clinical history, FAP knowledge, and effectiveness of the conference and presenters.

**Results:** Of the 50 conference attendees, 35 (70%) completed baseline assessments, and 32 (64%) completed the post-conference counterpart.

Respondents' median age was 51 (range: 24-72), and 66% were female. Nineteen (54%) indicated that they had FAP, of which 12 (63%) had undergone colorectal surgery. Fundic gland polyps, duodenal polyps, and desmoid tumors were present in 9 (47%), 11 (58%), and 3 (16%) affected participants, respectively. Hepatoblastoma, duodenal cancer, and osteomas were reported in 1 individual each. Regarding surveillance, 14 (74%) and 13 (68%) of the affected respondents received upper and lower GI surveillance at least once every 3 years, respectively. Participants indicated that among healthcare professionals, their primary sources of information on FAP were primary care physicians (n=15), surgeons (n=12) and/or genetic counselors (n=13). Additional sources of information included internet based resources (n=32), print materials (n=22), and/or other individuals familiar with FAP (n=27). Respondents scored on average 69% correct on a 14-item measure of FAP-related knowledge prior to the conference; post-conference responses showed a statistically significant increase in mean scores (mean=77%, p<0.05). Thirty-one of post-conference respondents (97%) agreed or strongly agreed with items affirming conference effectiveness. Most attendees stated that the FAP conference provided them with information critical to informed medical decision making. All respondents stated a desire to attend future FAP conferences.

**Conclusions:** Conference attendees represented the wide clinical spectrum of FAP, with most adhering to high-risk surveillance guidelines. While the majority of participants obtained their FAP-related information from the internet, they may benefit from improved educational efforts that encourage active participation in their own maintenance and treatment of FAP. Future conferences should be targeted to meet the broad range of patient interest and knowledge in FAP-related topics.

## P21

### The family history score tool identifies high risk families for colorectal cancer

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**Background:** Assessing family history risk of colorectal cancer (CRC) is often difficult due to complex permutations and combinations. A family

**Table 1 (abstract P21)**

| Screening Event/Year     | Scoring Range |           |                 |           |                   |          |                  |          | Total       |
|--------------------------|---------------|-----------|-----------------|-----------|-------------------|----------|------------------|----------|-------------|
|                          | 0<br>Avg Risk | %         | 1-7<br>Mod Risk | %         | 8-10<br>High Risk | %        | >10<br>High Risk | %        |             |
| Minority Health Fair '06 | 114           | 83        | 23              | 17        | 0                 |          |                  |          | 137         |
| Women's Health Fair '06  | 203           | 75        | 63              | 23        | 1                 | 1        | 3                | 1        | 270         |
| Minority Health Fair '07 | 130           | 83        | 23              | 14        | 3                 | 2        | 1                | 1        | 157         |
| Women's Health Fair '07  | 128           | 73        | 41              | 23        | 3                 | 2        | 3                | 2        | 174         |
| Minority Health Fair '08 | 66            | 86        | 10              | 13        | 0                 | 0        | 1                | 1        | 77          |
| CRC Awareness Month '08  | 116           | 47        | 115             | 46        | 7                 | 3        | 10               | 4        | 248         |
| Women's Health Fair '08  | 116           | 73        | 33              | 21        | 9                 | 5        | 1                | 1        | 159         |
| <b>Total</b>             | <b>873</b>    | <b>71</b> | <b>308</b>      | <b>25</b> | <b>23</b>         | <b>2</b> | <b>19</b>        | <b>2</b> | <b>1123</b> |

history score has been developed and validated to simplify familial risk assessment. This study examines the usefulness of this scoring system to identify families at risk through public outreach programs.

**Methods:** A published Family History Scoring System [1] was used to determine familial cancer risk at 7 health fair and educational events spanning 2006-2008. Patients with scores  $\leq 7$  are considered at moderate risk for advanced adenomas or CRC, scores with  $>7$  signify high risk, and scores  $>10$  are suggestive of a hereditary colorectal cancer syndrome. A computer program using touch screen technology was designed to record and calculate family history score and was used at the women's and men's health fairs. No identifying information was collected. Recommendations for surveillance were given depending on the risk level assigned.

**Results:** 1223 people participated. The scores are summarized in Table 1.

#### Reference

1. Church JM: Family History Scoring System. *Dis Col Rectum* 2005, **48**:889-96.

#### P22

##### Aggressive gastric cancer in a patient with an APC mutation and a monoallelic MYH mutation

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Familial Adenomatous Polyposis Syndrome (FAP) is an autosomal dominant inherited hereditary colorectal cancer syndrome that is characterized by hundreds to thousands of adenomatous colonic polyps and, without treatment and close surveillance, confers a high lifetime risk of colon cancer. Polyps usually develop in adolescence and virtually all will develop polyps by age 30. It is caused by a mutation in the Adenomatous Polyposis coli (APC) gene which is responsible for tumor suppression and controls apoptosis. While benign fundic gland polyps are common, gastric cancer is rare in the Western population. MYH Associated Polyposis Syndrome (MAP) is an autosomal recessive disease caused by biallelic mutations in the MYH gene which is part of the base excision repair system. Patients with MAP exhibit an attenuated form of polyposis with 10's to 100's of adenomatous polyps and have a later age of onset, typically 10 years later than FAP. Currently to be diagnosed with MAP patients must carry biallelic mutations though recent studies have described similar colon cancer risks for monoallelic carriers.

We report on a case of a 65 year old woman with an APC mutation positive FAP (de novo) who also carries a monoallelic mutation in the MYH gene G382D that developed metastatic gastric cancer within a year of a clear CT scan. She had undergone a colectomy with IRA in her 20's and had been followed by yearly endoscopic surveillance that demonstrated polyps in the remaining rectum as well as adenomatous duodenal polyps and gastric polyps with no evidence of malignancy. At 61 she was converted to a J-Pouch and continued with appropriate surveillance. At age 64 Spiegelman Stage III duodenal adenomatosis was detected and EGDs were done every 3 months. In March 2008 she presented to the ER with epigastric pain, hematochezia and hematemesis following an EGD and polypectomy earlier that day. A CT of the chest,

abdomen and pelvis did not reveal any abnormalities. She continued to be monitored every 3 months and in March 2009 she had progressed to Spiegelman Stage IV. Biopsies were obtained from the duodenal adenomas and were negative for high grade dysplasia. Two months later a CT scan revealed abnormal nodules in the liver. A diagnosis of metastatic gastric cancer was made following further studies.

#### P23

##### Impact of genetic testing on risk-reducing behavior in women at risk for hereditary gynecologic cancer syndromes

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**Background:** Women with hereditary breast and ovarian cancer (HBOC) have an estimated 15-65% lifetime risk of ovarian cancer; similarly, women with Lynch syndrome have a 40-60% lifetime risk of endometrial cancer and a 10-12% lifetime risk of ovarian cancer. The aim of this study was to investigate the impact of genetic testing on risk-reducing behavior for gynecologic malignancies in women being tested for HBOC and Lynch syndrome.

**Methods:** 190 women age  $\geq 30$  undergoing genetic testing for HBOC (N=102) or Lynch syndrome (N=88) completed questionnaires at baseline, 1 month, 3 months, and one year after testing. Women evaluated for HBOC were tested for germline BRCA1 or BRCA2 gene mutations; those evaluated for Lynch syndrome were tested for germline DNA mismatch repair (MMR) gene mutations. Subjects were asked about personal cancer history, prior surgeries, cancer screening practices, and genetic test results. Gynecologic cancer screening was considered adequate for the HBOC cohort subjects if they had a transvaginal ultrasound (TVUS) in the past 12 months. Adequate screening for Lynch cohort subjects was defined as having had a TVUS and endometrial biopsy in the past 12 months.

**Results:** Of the 190 women age  $\geq 30$  undergoing genetic testing, 145 subjects (87 HBOC; 58 Lynch) had no prior history of gynecologic malignancy, hysterectomy, or salpingo-oophorectomy (BSO) and were thus at risk for gynecologic cancer. Subjects' mean age was 45.4 years and 52% (74/141) reported a personal history of any cancer. At baseline, 40% (34/84) of subjects being tested for HBOC and 46% (26/57) of those tested for Lynch syndrome reported prior gynecologic cancer screening. One-year follow up questionnaires were available on 74 subjects (48 HBOC; 26 Lynch) none of whom had been diagnosed with a gynecologic cancer in the year following testing. 92% (11/12) of BRCA mutation-positive subjects had undergone either BSO (N=8) or screening with TVUS (N=3). None of the 6 BRCA mutation-negative subjects had prophylactic surgery or gynecologic cancer screening. Of those HBOC subjects with indeterminate or variant genetic test results, 27% (8/30) had either a BSO (N=3) or TVUS (N=5). 100% (5/5) of the MMR mutation-positive had undergone hysterectomy with BSO (N=2) or screening with TVUS and endometrial biopsy (N=3). None of the 3 MMR mutation-negative subjects

had prophylactic surgery or gynecologic cancer screening. Of those subjects with indeterminate or variant genetic test results, 17% (3/18) had screening; none had prophylactic surgery.

**Conclusions:** In the first year after genetic testing, women who tested positive for HBOC or Lynch syndrome increased uptake of prophylactic surgery or screening to reduce their risk of gynecologic cancers. Women with true-negative results do not pursue these unnecessary interventions, whereas those with indeterminate or variant test results do not significantly change their risk-reducing behaviors.

## P24

### Linking of Utah genealogies to outpatient colonoscopy records defines familial aggregation of colorectal polyps and cancer

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**Background:** The Utah Population Database (UPDB) is a shared research resource of the University of Utah. It combines Utah genealogies dating back to the 1700s with data from statewide resources, including a cancer registry, hospital claims, as well as birth and death certificates. A project completed in 2008 linked the UPDB to patient demographic records from Intermountain Healthcare which is a non-profit medical system that serves Utah and Southeast Idaho, providing care to approximately 60% of the resident population. The availability of large numbers of linked, electronically searchable medical records offers unique opportunities for improved clinical and outcomes research. We address the question of the extent to which colonic adenomas and hyperplastic polyps co-segregate with colon cancer risk in non-syndromic families.

**Methods:** A pilot project was initiated to use this new linked research infrastructure by ascertaining the occurrence of colorectal polyps from Intermountain clinical data. De-identified medical information was merged with UPDB family structure and statewide cancer data. These combined data sets provided family structure along with cancer histories to investigate familial aggregation. Cox Regression Analysis was used to assess the relative risk of (a) polyp development and (b) colon cancer for first-, second- and third-degree relatives, by polyp type. Custom kinship analysis tools allowed determination of the excess polyp and cancer risk observed in the kindreds of each case, and differentiated high-risk from population-risk families.

**Results:** The queries captured data from over 70,000 positive outpatient colonoscopy procedure and pathology reports from over 58,000 de-identified individuals examined between 1995 and 2009. The queries collected data on age, gender, polyp type, number, size, pathology and were verified by manual review of a randomly selected sample of 200 cases. We identified high-risk kindreds dating to founders born in the late 1700s, with high relative risks for polyp/cancer. Analysis of discrepancies between excess polyp and excess cancer risks within families allowed us to address the possibility that some cancers may arise in the absence of significant excess polyp risk.

**Conclusion:** The combination of a large, electronically searchable medical database (and associated tissue specimens) with a linked genealogical resource offers a powerful platform for the development of hypothesis-driven research.

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