Clinical and molecular aspects of MUTYH- and APC-associated polyposis

Nielsen, M.

Chapter 1

Introduction

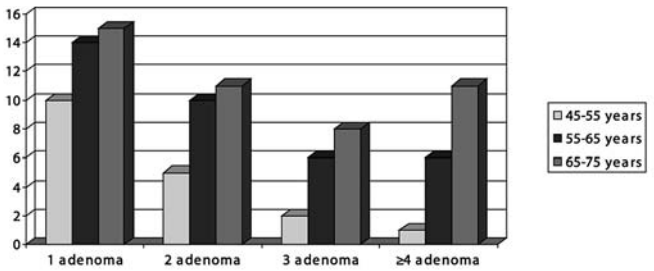
1.1

General introduction on polyposis syndromes

1.1 General introduction on polyposis syndromes

Polyps, in most cases colorectal adenomas, are the requisite benign precursor for colorectal cancer (CRC) and it has been theorized that one in 10 adenomas will ultimately progress to cancer.[1-3] In addition to adenoma size and grade of dysplasia, the chance of malignancy among these lesions grows with larger numbers of adenomas.[4, 5]
A relatively large proportion of the general population will develop one or more polyps (25% at age 50 and 50% at age 70) and are, therefore, at increased risk of developing CRC.[6,1] This is also illustrated with meta-analyses based on the literature[7-9] and the Dutch histopathology registry (Palga).

Figure 1 Age-specific stratification of the number of adenomas from autopsy reports (adapted from Geul KW. http://www.cbo.nl/product/richtlijnen/folder20021023121843/poliepectomie.pdf)



Indeed, colorectal cancer is at the moment the third most common malignancy and worldwide, colorectal cancer accounted for about one million of new cancers diagnosed in 2002, representing nearly 10% of all new cancers.[10] Survival estimates at 5-years is about 54% in Western Europe.[10] Since removing adenomas significantly reduces the chance at developing colon cancer,[3, 11] population based colon screening policies have been or are being installed in a number of (western) countries.
The causes of adenomas are multifactorial in most cases including environmental factors like diet, life style and specific commensal bacteria, and genetic factors. The identification of these genetic factors that confer individually small increases in risk is underway through genome-wide association studies and in the near future also total genome or exome sequencing. There are most likely hundreds of these low-penetrance cancer susceptibility genes, each contributing to only a small proportion of the total genetic component of risk.[12] Genetic factors particularly assumed to contribute to CRC risk in familial CRC cases, which compromise approximately 35% of all CRC cases.[13]

Only about 5% of CRC cases are actually associated with a highly penetrant dominant or recessive inherited syndrome, see figure 2.

Identifying such patients is important because this allows for improved prevention and care for those in the highest category of CRC risk. Since the risk for developing CRC is much higher, colon screening in these cases needs to be more frequent and to start at a much younger age than in the population. Furthermore, family members at risk should be identified and offered surveillance, preferable before they have developed CRC or other associated cancers.

The inheritable polyposis/CRC syndromes are defined and separated from each other by clinical and genetic criteria. In this introduction the various types of colorectal polyposis are discussed, including *APC* associated polyposis, attenuated FAP, *MUTYH*- (formerly annotated as *MYH*-) associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), Cowden syndrome (CS), hyperplastic polyposis syndrome (HPS) and hereditary mixed polyposis syndrome (HMPS). See also table 1 for a short overview of all the syndromes and their clinical and genetic aspects.

APC associated polyposis

APC associated polyposis is an autosomal dominant inherited disease caused by germline mutations in the *APC* gene located on chromosome 5q21; it affects approximately two to three in 100,000 individuals.[14-16] Originally, the term *familial adenomatous polyposis,* (FAP, OMIM 175100), was used to describe *APC* positive and negative patients, based on a clinical phenotype of more than a hundred polyps. Since it became clear that FAP patients can also have mutations in other genes, like *MUTYH* discovered in 2002, the term *APC-associated polyposis (AAP)* for patients with proven *APC* mutations seems more appropriate.

Less than 1% of all cases of CRC are attributed to *APC*-associated polyposis. This low figure reflects the rarity of the condition but is also due to cancer prevention in

Figure 2

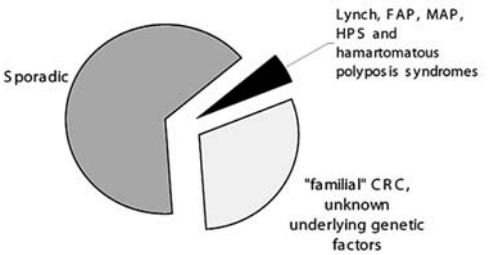


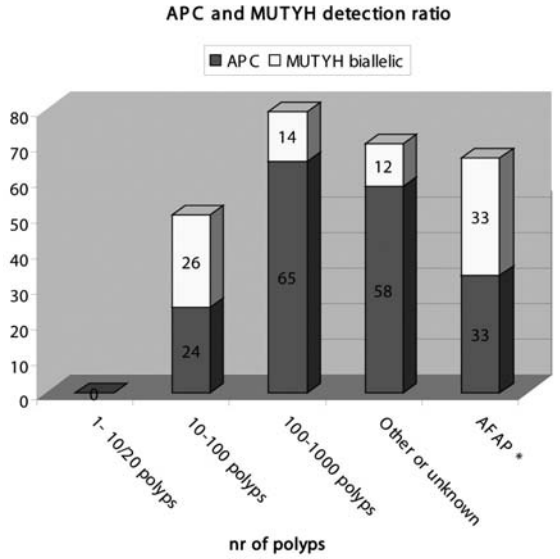
Table 1 Polyps and CRC syndromes

Syndrome	Clinic	Histology polyps	Extracolonic features
APC associated polyposis	Between 100- 5000 colonic polyps. Age at diagnosis: 34-42 yrs in symptomatic and 22 yrs in asymptomatic persons. Cumulative CRC risk 100% at age 35-40 yrs without surveillance.	Mainly adenomas, hyperplastic polyps and serrated adenomas may occasionally be diagnosed.	Duodenal/pancreas carcinoma, papillary thyroid carcinoma, medulloblastoma CNS, hepatoblastoma of the liver. Benign: osteomas, dental abnormalities, CHRPE, epidermoid cysts and lipoma, desmoids tumors and adrenal masses.
MUTYH associated polyposis	Between 10 and 500 polyps, CRC risk 40-100%. Mean age CRC: 49 yrs. CRC and no/few polyps have been described in some patients.	Adenomas and hyperplastic polyps.	A higher risk has been reported for: duodenal (4% cumulative risk), ovarium, bladder carcinomas and skin cancer. Sebaceous gland tumors in ± 2%. Few cases with lipomas, CHRPE, osteomas, jaw-bone cyst, epidermoid cyst and pilomatrixomas.
Attenuated polyposis	Age at CRC: 50-60 yrs. CRC risk at age 80 yrs: 69%	Adenomas.	Depending on the underlying genetic defect
Lynch syndrome	CRC cumulative risk 43-69% at median age 42-47 (risk and age depends on gender and MMR mutation).	Adenomas.	Cancers of the endometrium (39-60% risk for women), ovary (10-12%), stomach (13%), small intestine, hepatobiliary tract, upper urinary tract, brain, and skin.
Peutz-Jeghers syndrome	Median age of onset: 10-13 yrs (wide range). Polyps most prevalent in small intestine but also occur in the stomach and large bowel. Complications: intus-susception and bleeding. High risk for gastrointestinal cancer.	PJS polyps. Adenomas may occur.	Mucocutaneous pigmentation, Colorectal, gastric, pancreatic, breast, and ovarian cancers. Females are at risk for sex cord tumors with annular tubules (SCTAT), adenoma malignum of the cervix. Males can develop calcifying Sertoli cell tumors.
Juvenile polyposis	Most patients have some polyps at age 20. Usually between 5 and 200 polyps.	JPS polyps. Adenomas may occur.	Gastric, duodenal, and pancreatic tumors. Hereditary hemorrhagic telangiectasia (HHT).
PTEN polyposis syndromes: Cowden and Bannayan-Riley-Ruvalcaba syndrome (BRRS)	Symptoms usually occur during the 2nd and 3rd decade but may be diagnosed as early as 4 yrs or as late as 75 yrs of age.	Small and nodular, the expanded lamina propria is more myofibroblastic than edematous.	Cowden: Tumors of breast and thyroid, autoimmune thyroiditis, trichilemmomas, and papillomatous papules, macrocephaly, and mental impairment. BRRS: macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis.
Hereditary mixed polyposis syndrome	Polyps: 28-32 (youngest case 10 yrs), CRC: 40-65 yrs.	Adenomas (classic, serrated and tubular), hyperplastic polyps, juvenile polyps, and mixed juvenile-aden. or hyperplastic-aden.polyps	Thyroid cancer and a Wilms tumor in affected individuals with an *BMPR1A* mutation.
Hyperplastic polyposis syndrome	Median age at diagnosis: 44 yrs (range 27-78 yrs) CRC in 36%-67% at 57 yrs.	Hyperplastic and (serrated) adenomas	None

Syndrome	Associated genes	Prevalence	penetrance
APC associated polyposis	*APC*	2-3:100.000, 0,5-1% of CRCs, 10-20% de novo	100%
MUTYH associated polyposis	*MUTYH*	1:10,000, 1% of CRCs	100%
Attenuated polyposis	*APC and MUTYH*	10% of polyposis families	ND
Lynch syndrome	*MLH1, MSH2, MSH6* and *PMS2*	Beween 1:2000 and 1:660, 1-3% of CRCs 6% of CRC younger than 50 yrs	50-80%
Peutz-Jeghers syndrome	*STK11 (LKB1) in 94%*	1/8,300 to 1/280,000,± 50% de novo	93% cancer risk at age 65
Juvenile polyposis	*SMAD4, BMPR1A, PTEN* or *ENG-genes. Total 30-50%* detection ratio	1:16.000-1:100.000, ± 25-50% de novo	39% cumulative life-time risk for CRC
Cowden and BRRS	*60-80% PTEN* and rarely *SDHB*	1:200.000	penetrance close to 100% at age 30 yrs
Hereditary mixed polyposis syndrome	*BMPR1A in 50%.* Linkage to 15q13-14 in Ashkenazi families	Rare	ND
Hyperplastic polyposis syndrome	*SMAD4 and MUTYH*	1:2000	ND

CRC= colorectal cancer, yrs= years, CHRPE=congenital hypertrophy of the retinal pigment epithelium.

Table 2



* as described by Nielsen *et al* 2007

known affected subjects. Mutation carriers are predisposed in the majority of cases to develop hundreds or even thousands of polyps during childhood and adolescence and subsequently go on to develop CRC.[17] Most have already developed numerous polyps in their twenties making a colectomy at a relative young age necessary. Without surgical intervention FAP patients almost inevitably develop CRC by the mean age of 40–50 years.

The *APC* gene is a relatively large gene, encompassing 15 exons and encodes a protein of 2843 amino acids. Exon 15 is by far the largest exon, containing over three-quarters of the coding sequence. The *APC* gene codes for a multifunctional protein that comprises several motifs and domains, allowing it to bind and/or interact with multiple molecules that include β-catenin, α-catenin, GSK3β, axin, conductin, and tubulin.[18] Over 700 different disease-causing mutations have been reported throughout the *APC* gene, but most mutations occur in the 5' half of the coding region of exon 15, otherwise referred to as the mutation cluster region. Hotspot mutations are found at codon 1061 and 1309. Depending on clinical features and mutation detection techniques applied, mutations in the *APC* gene can be identified in approximately 70% of patients with more than a 100 polyps (see table 2). A list of mutations is available online at the *Leiden Open Variation Database* (LOVD): http://chromium.liacs.nl/LOVD2/colon_cancer/home.php?select_db=*APC*. The most common germline mutation involves the introduction of a premature

stop codon, either by a nonsense mutation, frameshift mutation, small deletion or insertion. With Multiplex Ligation-dependent Probe Amplification (MLPA), introduced in 2002, partial and whole gene deletions have been found in a substantial proportion (4–33%) of patients previously tested negative for *APC* mutations.[19, 20,21] About 10-25% of *APC* mutations occur de novo[22]and with more sensitive techniques it has been shown that in 11-21% of these de novo cases, *APC* mosaism is present in a parent or proband. [23, 24] Differences in phenotype may relate to the location of the mutation within the *APC* gene.
An intermediate phenotype (i.e. 100 to thousands of polyps) is associated with mutations in codon 157–1595, excluding the mutation cluster region. Mutations occurring between codon 1250 and 1464 but particularly at codon 1309 lead in most cases to a more profuse type of polyposis (>5000 polyps) with earlier age of CRC onset.[25]A more attenuated form of polyposis is associated with mutations in three regions: (i) in the 5' part of the *APC* gene; (ii) alternatively spliced region in exon 9 and (iii) mutations in the extreme 3' site of the gene.[25] See also the next section on AFAP.

The majority of FAP patients, over 70%, develop extracolonic manifestations.[26] Extracolonic manifestations are variably present and include lesions with less clinical significance such as congenital hypertrophy of retinal pigmented epithelium (CHRPE), dental abnormalities (absences of teeth amongst others), duodenal and gastric adenoma, fundic gland polyps, osteomas, adrenal masses (mostly adrenocortical adenomas without endocrinopathy) and epidermoid cysts or lipomas on any part of the body.[25, 27, 28] Other manifestations cause serious complications and can be a cause of death such as malignant lesions in the duodenum, thyroid carcinoma (papillary, the Cribriform-Morular variant,) and brain (usually medulloblastoma), liver (hepatoblastoma) and desmoid tumours.[25, 26, 29, 30]

Two variants of *APC* associated polyposis syndromes exist in which patients have an specific extracolonic tumour spectrum besides their polyposis, namely osteomas and soft tissue tumours including desmoids and thyroid tumours in Gardner syndrome and central nervous system (CNS) tumours in Turcot syndrome.[30] Central nervous system (CNS) tumours are also found in patients with Lynch syndrome.
Because of the high CRC risk, a life long strict endoscopic surveillance is recommended for patients with an *APC* mutation or at-risk family members that refrain from genetic testing. At a Mallorca consensus meeting in 2006-2007 starting endoscopic surveillance from age 10-12 years was advised at an interval of 2 years.[31] Surveillance can start with a sigmoidoscopy and if adenomas are detected, there is an indication for full colonoscopy

to be performed annually. In symptomatic patients, endoscopic investigation may be indicated at any age. Colectomy is advised once polyps are too numerous to be safely managed endoscopically or adenomas with advanced histology have occurred. Most patients with classical FAP undergo surgery between age 15 and 25 years. Continued surveillance of the rectal remnant or ileoanal anastomosis is necessary because of persistent risks of adenomas and carcinomas within residual mucosa. Also screening of upper gastrointestinal tract is recommended , starting at age 25-30 years with screening intervals depending on the polyp burden.[31] In high risk members (first-degree relatives of affected patients) from families without an identified *APC* mutation, surveillance should be continued at 2-yearly intervals until age 40. After this age, with negative screening results, the intervals between examinations may be longer -for example, every 3-5 years- and high frequent surveillance may be discontinued at age 50.[31]

MUTYH-associated polyposis (MAP)

In 2002, after identifying somatic G>T transversions (especially GAA>TAA) in the *APC* gene in adenomas from germline *APC* mutation negative polyposis patients, another form of polyposis has been discovered in a Welsh family. Al-Tassan *et al*. found germline mutations in the DNA base excision repair *MUTYH* gene and this new entity is now coined as *MUTYH*-associated polyposis (MAP, OMIM No 608456). MAP is an autosomal recessive condition. See also the review on MAP in chapter 2 of this thesis.

Most carriers of biallelic *MUTYH* mutations described to date developed between 10 and 500 polyps but also a number of MAP patients have been described with CRC and no or only a few polyps. The CRC risk in MAP patients is about 43% at age 60 and the life time risk is assumed to be close to 100% in the absence of timely surveillance.[32, 33] The life time risk for duodenal cancer is about 4% and a significantly increased incidence has been shown for ovarian, bladder and skin cancer (SIR 5.7, SIR 7.2 an SIR2.8). Sebaceous gland tumours, also found in patients with Lynch syndrome, are found in about 2% (chapter 2.3).

MAP is found in 10–20% of polyposis patients, see table 2. In patients with CRC and no or only a few polyps the possibility of MAP should be considered by the pathologist, especially when a hotspot *KRAS2* codon 12 GGT>TGT (c.34 G>T transversion in exon 1) mutation is present, see figure 3. Adenomas as well as hyperplastic polyps can be present in MAP patients.[34] Cancers of the colon are often right-sided and multiple at presentation. Colonic screening should start at age 18-20 years and gastroduodenal screening at age 25-30 years.[31] The spectrum and age of presentation of extraintestinal tumours does not support other forms of screening at the moment (chapter 2.3).

AFAP

Attenuated familial adenomatous polyposis (AFAP) is a clinically defined entity with a diverse genetic background. In most studies AFAP is defined as the development of less than a hundred polyps at a relatively late age.[35-37] However, the number of polyps is strongly influenced by age. We therefore defined revised criteria for this phenotype (see also chapter 5), there should be (1) at least two patients with 10–99 adenomas at age >30 years or (2) one patient with 10–99 adenomas at age >30 years and a first-degree relative with CRC with few adenomas; for both criteria, no family members with >100 adenomas before the age of 30 years. According to these criteria about 36% had mutations in the *APC* gene and biallelic *MUTYH* mutations were found in also 36%. In the remaining 28% no germline mutations were found. The age at diagnosis of CRC in AFAP families with an *APC* mutation was 10–15 years later than in classical FAP (54 years versus 30 years). In a study of a large family with AFAP, no CRC was observed in patients under the age of 29 years.[38] Screening in families with AFAP periodic examination is recommended to start from age 18-20 years,[31, 39] which is at a later age than recommended for classic FAP patients (10-12 years).

Lynch syndrome

Lynch syndrome (previously annotated as hereditary non-polyposis colorectal cancer, OMIM No 114500) is an autosomal dominantly inherited predisposition characterized by the early development of colorectal cancer, endometrial cancer and various other cancers. Lynch syndrome is thought to be responsible for 1-3% of all CRC cases.[40] In Lynch syndrome, patients develop only about 1 to 10 adenomatous polyps, but these polyps develop relatively fast in cancer. Colorectal carcinoma is characterized by early age at onset, predominantly right sided with an excess of synchronous and metachronous tumours. CRC present between 20 and 70 years of age. Survival rates after cancer appear to be better in Lynch CRC patients than in sporadic patients to some authors, but this is disputed by others.[41-43]

All Lynch patients have a high risk for developing cancer, though the age at diagnosis and penetrance differs according to the underlying genetic defect. The spectrum of associated carcinomas is broad and includes endometrial carcinoma and ovary carcinoma, urinary tract carcinomas, stomach, small bowel and biliary tract carcinoma, and brain tumours.[44]

Two variants of Lynch syndrome exist in which patients develop specific extracolonic lesions, namely sebaceous gland tumours in Muir Torre syndrome and brain tumours in Turcot syndrome.

Germline mutations in four genes coding for components of the mismatch repair

Table 3 Amsterdam criteria II and revised Bethesda guidelines

Amsterdam criteria II	Revised Bethesda guidelines
• There should be at least three relatives with colorectal cancer (CRC) or with a Lynch syndrome-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis. • one relative should be a first-degree relative of the other two, • at least two successive generations should be affected, • at least one tumour should be diagnosed before the age of 50 years, • FAP should be excluded in the CRC case if any, • tumours should be verified by histopathological examination.	• CRC diagnosed in a patient aged <50 years, and/or • Presence of synchronous, metachronous colorectal or other Lynch syndrome-related tumours,* regardless of age, and/or • CRC with MSI-H@ phenotype diagnosed in a patient aged <60 years, and/or • Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed at age <50 years, and/or • Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumour, regardless of age.

* Lynch syndrome-related tumours: cancer of the endometrium, small bowel, ureter or renal pelvis. @ MSI-H phenotype: microsatellite instability high

machinery are associated with Lynch Syndrome: *MSH2* located in 2p22-p21, *MLH1* located in 3p21.3, *MSH6* located in 2p16 and *PMS2* located in 7p22. Most mutations (up to 80%) have so far been found in the *MLH1* and *MSH2* genes.[45] These four MMR genes act in co-operation enabling the recognition of DNA mismatch and repair during DNA replication. A defect in the MMR system leads to small deletions and insertions in coding and non-coding stretches of short repetitive DNA sequences called (microsatellites) distributed throughout the genome; this is called microsatellite instability (MSI). A high microsatellite instability can be found in >90% of colon cancers associated with Lynch syndrome, whereas in sporadic CRC it is found in approximately 15% of cases. With immunohistochemical (IHC) analysis using antibodies against the four MMR proteins, loss of protein expression of the causative gene can be shown.

In 1989, the Amsterdam criteria were formulated to provide more uniformity in the families for international collaborative studies. In 1999, these criteria were revised and now include various extra-colonic tumours. Families that meet the original Amsterdam criteria but do not have evidence for MMR deficiency should be referred to as having Familial colorectal cancer type X and not Lynch syndrome.[46]

The less restrictive revised Bethesda guidelines are being used for selecting families for molecular analysis of tumours, including MSI and immune histochemistry analysis.[44] Table 3 shows the revised Amsterdam criteria and Bethesda guidelines. The sensitivity of MSI analysis for detecting MMR defects varies between 80-90% and that of IHC analysis between 73-87% depending on whether clinical selection criteria were used or not.[40] The advantage of IHC is that it may direct mutation analysis because the pattern of staining is suggestive of the underlying gene defect.

In April 2006, the Mallorca-group recommended that surveillance should start between age 20 and 25 years. Full colonoscopy to the cecum is recommended every one to two years. Upper age limit of surveillance depend on the patient's general state of health and should be made on an individual basis. Surveillance by gynaecological examination, transvaginal ultrasound and aspiration biopsy of the endometrium starting from age 30–35 years may lead to the detection of premalignant lesions and early cancers, but the value of this surveillance is still largely unknown. Prophylactic hysterectomy and salpingo-oophorectomy may be an option for women with Lynch syndrome, since it substantially reduces site-specific cancers.[44]

Hamartomatous polyposis syndromes

The hamartomatous polyposis syndromes together account for <1% of colorectal cancer and include Peutz-Jeghers syndrome, juvenile polyposis syndrome and the *PTEN hamartoma tumour syndromes* Cowden's syndrome and Bannayan-Riley-Ruvalcaba syndrome. While the diagnosis of these inherited syndromes is primarily clinical, genetic testing is now available for all these syndromes. Hamartomatous polyps are characterized by the observation that there is not only expansion of epithelial cells but also of stroma cells, the latter sometimes even more extensive.

Peutz-Jeghers syndrome (PJS, OMIM 175200)

The autosomal dominant inherited polyposis syndrome Peutz-Jeghers syndrome (PJS,) is characterised by the occurrence of mucocutaneous pigment spots and hamartomatous polyps and an increased risk of various cancers. Peutz-Jeghers-type hamartomatous polyps are most common in the small intestine but can also occur in the stomach and large bowel.[47]

The PJS polyps are typically multilobulated with a papillary surface and grossly resemble tubulovillous adenomas. The epithelium covers a core of arborizing smooth muscle.[48]

The diagnosis of PJS is based on clinical and histological criteria, including the presence of (1) one PJS polyp along with a positive family history of PJS (2) one PJS polyp and classical pigmentation or (3) two or more PJS polyps/small-bowel polyposis.[49]

The disease has a variable penetrance-even within families; some members will only manifest with hyperpigmentation, while others manifest with pigmentation and intestinal polyps. PJS polyps usually become symptomatic in the first or second decade of life, but onset can occur from the first year of life to old age. In a cohort of 31 patients, complications occurred before the age of ten years in 42% of patients.[50]

Common manifestations are invagination or obstruction of the small bowel as well as occult gastrointestinal bleeding resulting in iron deficiency anaemia. PJS patients are

furthermore at increased risk of developing cancer at several organ sites, and there is a significantly increased risk that patients with PJS will die of cancer at a young age. An overall cumulative risk for all cancer of 37-93% has been reported in patients with PJS.[51] The highest cumulative risk has been reported for breast cancer (32-54% in females) and CRC (39%). Other cancer entities include carcinomas in the stomach, small intestine, pancreas, lung, uterus, ovary, testis (Sertoli cell tumours), and cervix (adenoma malignum).[51] Using sequence analysis and MLPA, germline mutations of the serine–threonine protein kinase 11 (*STK11*) gene on locus 19p13.3 can be detected in up 94% of patients.[52] STK11 regulates cell division, differentiation and cellular signal transduction. One study found that the phenotype was more severe in families with a truncating mutation than a missense or no mutation.[50] Another –larger- study did not find statically significant differences between these two groups however.[53] Regular surveillance is recommended once the diagnosis of PJS is established.

Surveillance endoscopy (double-balloon enteroscopy) and polypectomy decreases the frequency of bowel obstruction and need for emergency surgeries and is recommended to start at age 8-10 years. [50, 51, 54 55] At age 20 years screening with gastroduodenoscopy should be started, also for detection of (non-malignant) hamartomas, in view of the morbidity caused by complications of these lesions.[51] Colonoscopy is recommended to start at age 25 years. Pancreatic surveillance using endoscopic ultrasound and/or MRI is also advised. For female PJS patients, breast exam and MRI pelvis are advised starting from age 25. Furthermore regular transvaginal ultrasound, cervical smear, pelvic exam and CA-125 measurement has been proposed. For males with PJS, regular clinical examination of the testis is recommended. It is yet unclear whether surveillance in PJS patients actually decreases morbidity and mortality.[54]

Juvenile polyposis syndrome (JPS, OMIM 174900)

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant disorder characterized by multiple (5-200) juvenile polyps in the gastro-intestinal tract, primarily affecting the colorectum. Juvenile polyps are characterized by an overgrowth of an oedematous lamina propria containing glands showing cystic dilatation (mucous retention cysts) and occasionally a serrated architecture.[48] The number of polyps is variable between individuals, also in the same family, some have only few polyps while others have more than 100 polyps. Polyps usually occur by the third decade of life.

Criteria for establish the diagnosis are: more than 5 juvenile polyps of the colorectum, or multiple juvenile polyps throughout the gastrointestinal tract (OR upper and lower GI tract) or any number of juvenile polyps with a family history of juvenile polyposis.[56]

Most juvenile polyps are benign; however they may cause bleeding and anaemia and

malignant transformation can occur. The highest risk for a malignancy is in the colon, with a cumulative risk of approximately 40%. [57,58] Gastric, duodenal, and pancreatic tumours have also been reported but are less common than colorectal carcinomas.[56, 59, 60] Howe *et al* reported a 20% risk for gastric cancer when gastric polyps are present.[61] A combined syndrome of JPS and hereditary hemorrhagic telangiectasia (HHT) may be present in 15-22% of individuals with a SMAD4 mutation.[62]

Approximately 75% of individuals with JPS have an affected parent, 25% of probands with JPS have no previous history of polyps in the family and may have a de novo mutation. Germline point mutations and large deletions are found in *SMAD4* on chromosome 18q21 in approximately 20-35% in *BMPR1A* gene on chromosome 10q23 in approximately 20-25%, [63,62 Howe 2004] in *PTEN* on chromosome 10q23 2,5% [62] and *ENG* on chromosome 9q33 was reported in only two patients.[64]

General guidelines for surveillance were proposed by Howe and others which stated that, in patients at risk for JPS, colonoscopic screening should start at age 15 or earlier if the patient is having symptoms. [58, 65] If screening reveals no polyps, it should be repeated every 3 years. When colorectal dysplasia is present or many polyps are identified, removal of most or part of the colon may be necessary.[58, 65] Furthermore, upper endoscopic screening and evaluation of the small intestine has also been advised.[49]

PTEN hamartoma tumour syndromes: Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (B-R-RS).

The *PTEN hamartoma tumour syndromes* Cowden and BRRS have historically been categorized as CRC predisposing cancer syndromes. However their CRC initiating ability might be questioned since only one patient with Cowden syndrome and CRC[66] has been published and none for BRRS patients. Cowden syndrome is a rare autosomal dominant syndrome which and is characterized by oral, cutaneous and gastrointestinal hamartomas, tumours of breast and thyroid, autoimmune thyroiditis, macrocephaly and developmental delay. It has a high penetrance (close to 100% by the age of 30 yrs) and is highly variable expressivity (between and within families). Clinical manifestations usually occur during the 2nd and 3rd decade but may be diagnosed as early as 4 years or as late as 75 years of age.[67] See for recent clinical criteria a review by Pilarski *et al* and Eng *et al*.[68 69] Polyps can occur anywhere in the gastrointestinal tract, but are not defining feature. Several varieties of the hamartomatous polyps are seen, including ganglioneuromatous lesions [70]and hyperplastic polyps[64] but a formal analysis of prevalence has not been done. Breast cancer is the most serious complication of Cowden's syndrome and affected about 22% of female patients in one study.[67] The life time risk of developing thyroid cancer is around 3 to 10%. [71] The underlying mechanism

is germline mutation of the *PTEN* gene on chromosome 10q23. Mutations in *PTEN* also account for the Bannayan-Riley-Ruvalcaba (BRR) syndrome (Omim 153480) which is characterized by macrocephaly, developmental delay, intestinal polyposis, lipomas, and pigmented macules of the glans penis. Intestinal polyps affects up to 45% of these patients. Polyps in BRR syndrome are histologically similar to the JPS polyp.[72]

Hyperplastic polyposis syndrome (HPS)

Hyperplastic polyps are one of the most common lesions of the large bowel, with a prevalence of 5%-11% seen at autopsy.[8 73, 74] Hyperplastic polyposis syndrome (HPS) is a relative recently described entity characterized by the presence of multiple hyperplastic polyps spread throughout the colorectum.[75] Previously thought to be completely benign, now compelling evidence shows the possibility of malignant development in hyperplastic polyps and numerous patients with CRC and concurrent HPS have been reported.[76]According to the WHO International Classification of Tumour definition[77] HPS should be diagnosed in an individual when the following criteria are present: (1) at least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which two are greater than 10 mm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with HPS, or (3) greater than 30 hyperplastic polyps but distributed throughout the colon. In a review of HPS, Jass *et al* found that the cumulative CRC risk is 36% in larger case series and 69% in single case reports.[48] A median age at diagnosis of 44 years (range 27-78) was found in one study of 38 HPS patients, CRC was present in 26% (10/38).[77]Another study found a somewhat later median age at diagnosis of 56 years (range 36-75) in 77 HPS patients.[78] CRC was diagnosed in 35% of these patients and in 52% the location of the CRC was proximal.[78] HPS has not been reported to be associated with polyposis outside the colon or with extra-colonic cancers.

Other polyp types are also frequently observed in HPS including adenomas and serrated adenomas.[76] It has been suggested that the pathway to colorectal cancer formation is through serrated polyps, which are believed to possibly arise directly from hyperplastic polyps. [78-80]

A genetic basis for hyperplastic polyposis has yet to be elucidated. A positive family history for CRC has been reported in 27-50% of cases [77, 81, 82] but a family history of hyperplastic polyposis syndrome is uncommon (2/38 families).[77] Molecular analysis of hyperplastic polyps or sessile serrated adenomas shows frequent somatic mutations in *BRAF* or *KRAS* and DNA methylation of different tumour suppressor genes.[81, 83, 84]A genetic predisposition to DNA methylation has been suggested since extensive methylation in the normal mucosa in HPS subjects has been found.[83]

A colonoscopy every 1-3 years for individuals with HPS, the interval depending on the number, size, and histology, and the ability to ablate both the hyperplastic and adenomatous polyps is suggested.[76, 77] However, the optimal treatment and surveillance protocol for HPS patients is largely speculative and might not be sufficient to prevent interval CRC because the miss rates for hyperplastic polyps and sessile serrated adenomas are likely to be higher than for adenomas.[78] In this respect advanced polyp detection techniques such as chromoendoscopy and narrow band imaging may be of additional value in HPS. Boparai *et al* suggested furthermore that if detection of and removal of all polyps is not feasible, surgical resection should seriously be considered.[78] Colectomy may be justified in those with a high number of HPs, concomitant serrated adenomas, or multiple high-risk adenomatous lesions (more than 1 cm, villous component, high-grade dysplasia).[82]

Although precise risk estimates are not possible based on current data, Chow *et al* also recommends surveillance of first-degree relatives of affected individuals beginning at age 40 (or 10 years earlier than the earliest age at diagnosis in the family).[77] A surveillance interval of five years has been recommended for relatives if no polyps are found.

Hereditary mixed polyposis syndrome (HMPS)

The HMPS is a rare condition, described in only few families world wide. It was first defined in a family in 1997.[85] Polyp numbers generally range from 1 to 15 and rarely exceed 50. The histological composition of polyps varies considerably from subject to subject, even within the same family. A mixture of colorectal polyps, including adenomas (classic, serrated and tubular), mixed hyperplastic polyps and mixed juvenile polyps, is present in the colon or rectum. [86, 87] The mean age of polyp presentation has been reported at 28 and 48 years,[86, 87] with the youngest age of polyp presentation being 10 years of age.[86] Colorectal cancer was diagnosed at ages between 40 and 65 years.[86] The primary concern for cancer in persons with HMPS is colon cancer, although two affected individuals have been reported with thyroid cancer and a Wilms tumour[87]

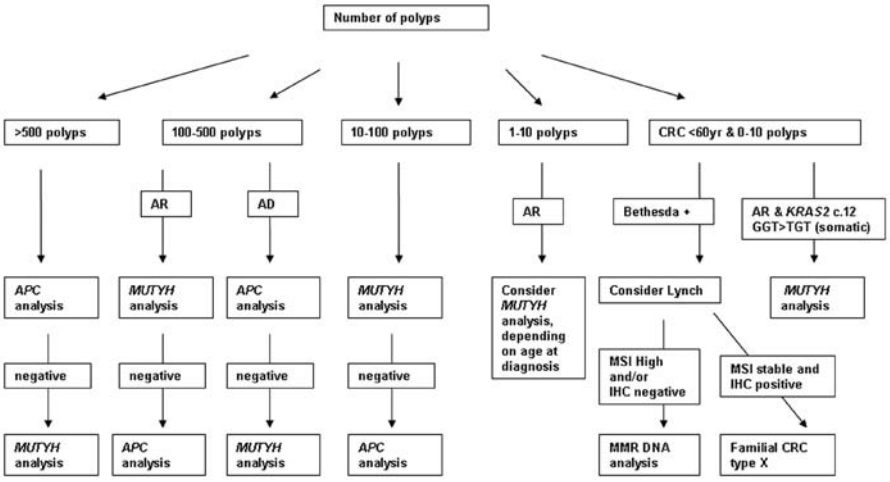
HMPS appears to be inherited as an autosomal dominant trait. Linkage analysis showed linkage to 15q13-14[86] in families of Ashkenazi ancestry. Recently, Cheah *et al* found germline exon deletions in the *BMPR1A* –gene on chromosome 10q23 in 50 % (4/8) of the HMPS families.[87] This study included a family previously reported by Cao *et al*.[88]A specific starting age and interval for colonoscopic surveillance in individuals with HMPS has not yet been defined. Participants in the 2003 Rozen *et al*. study[86] were offered colonoscopy with polypectomy every 1-2 years starting at age 20. Colectomy should also be considered if cancer occurs or the polyps cannot be managed through polypectomy.

Conclusion

Evaluation of highly penetrant CRC syndromes is of great importance because it has improved the understanding of sporadic CRC[12] and CRC syndromes contribute significantly to the burden of CRC especially in young (i.e.<50years) persons. Genetic testing and colorectal surveillance reduces cancer-specific deaths in these families.[89, 90] Identifying patients with heritable forms of CRC syndromes with or without polyps is elaborative and time consuming and involves the cooperation of several medical specialists. An accurate description of the phenotype by the gastro-enterologist, pathologist and clinical geneticist is pivotal to the establishment of a tumour syndrome diagnosis. A comprehensive description of polyp size, gross appearance, number, location, histology is needed and a personal and family history should be obtained whenever possible including information with respect to extra-colonic pathology.

Furthermore, molecular tests such as MSI, additional MMR IHC and *KRAS* mutation analyses, which are readily applicable and straightforward, can assist in establishing a diagnosis. Finally, diagnostic certainty can be obtained with molecular genetic testing in the germline. In figure 3, a decision tree is depicted for deciding in which gene molecular genetic testing should be done. In a number of families with many characteristics of a hereditary tumour syndrome of CRC and/or polyposis the genetic cause is yet unidentified. New techniques, such as whole exome or total genome sequencing may help to identify additional CRC/polyp predisposition genes.

FIGURE 3 Differential Diagnosis



Consider JPS, PJS, Cowden, BRRS, HPS or HMPS only when charecteristic clinical features and histological features are present (see table 1)

AR: autosomal recessive, AD: autosomal dominant, MMR: mismatch repair genes, PJS: Peutz-Jeghers syndrome, JPS: Juvenile polyposis, BRRS: Bannayan-Riley-Ruvalcaba syndrome, HPS: Hyperplastic polyposis syndrome HMPS: Hereditary mixed polyposis syndrome

References

1. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996;87:159-170.
2. Vogelstein B, Kinzler KW. The multistep nature of cancer. Trends Genet 1993;9:138-141.
3. Winawer SJ, Zauber AG, Ho MN *et al*. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981.
4. Stryker SJ, Wolff BG, Culp CE *et al*. Natural history of untreated colonic polyps. Gastroenterology 1987;93:1009-1013.
5. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658-662.
6. Imperiale TF, Wagner DR, Lin CY *et al*. Results of screening colonoscopy among persons 40 to 49 years of age. N Engl J Med 2002;346:1781-1785.
7. Arminski TC, McLean DW. INCIDENCE AND DISTRIBUTION OF ADENOMATOUS POLYPS OF THE COLON AND RECTUM BASED ON 1,000 AUTOPSY EXAMINATIONS. Dis Colon Rectum 1964;7:249-261.
8. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer 1982;49:819-825.
9. Bombi JA. Polyps of the colon in Barcelona, Spain. An autopsy study. Cancer 1988;61:1472-1476.
10. Parkin DM, Bray F, Ferlay J *et al*. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
11. Jorgensen OD, Kronborg O, Fenger C. The Funen Adenoma Follow-up Study. Incidence and death from colorectal carcinoma in an adenoma surveillance program. Scand J Gastroenterol 1993;28:869-874.
12. Ponder BA. Cancer genetics. Nature 2001;411:336-341.
13. Lichtenstein P, Holm NV, Verkasalo PK *et al*. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78-85.
14. Burn J, Chapman P, Delhanty J *et al*. The UK Northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. J Med Genet 1991;28:289-296.
15. Bulow S, Faurschou NT, Bulow C *et al*. The incidence rate of familial adenomatous polyposis. Results from the Danish Polyposis Register. Int J Colorectal Dis 1996;11:88-91.
16. Bjork J, Akerbrant H, Iselius L *et al*. Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. Scand J Gastroenterol 1999;34:1230-1235.
17. Bussey HJR. Familial Polyposis Coli: Family Studies, Histopathology, Differential Diagnosis, and Results of Treatment. Baltimore: 1975.
18. Lipton L, Tomlinson I. The genetics of FAP and FAP-like syndromes. Fam Cancer 2006;5:221-226.
19. Sieber OM, Lamlum H, Crabtree MD *et al*. Whole-gene *APC* deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas. Proc Natl Acad Sci U S A 2002;99:2954-2958.
20. Aretz S, Stienen D, Uhlhaas S *et al*. Large submicroscopic genomic *APC* deletions are a common cause of typical familial adenomatous polyposis. J Med Genet 2005;42:185-192.
21. Nielsen M, Bik E, Hes FJ *et al*. Genotype-phenotype correlations in 19 Dutch cases with *APC* gene deletions and a literature review. Eur J Hum Genet 2007;15:1034-1042.
22. Aretz S, Uhlhaas S, Caspari R *et al*. Frequency and parental origin of de novo *APC* mutations in familial adenomatous polyposis. Eur J Hum Genet 2004;12:52-58.
23. Aretz S, Stienen D, Friedrichs N *et al*. Somatic *APC* mosaicism: a frequent cause of familial adenomatous polyposis (FAP). Hum Mutat 2007;28:985-992.
24. Hes FJ, Nielsen M, Bik EC *et al*. Somatic *APC* mosaicism: an underestimated cause of polyposis coli. Gut 2008;57:71-76.
25. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in *APC* and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol 2007;61:153-161.

26. Bertario L, Russo A, Sala P *et al*. Genotype and phenotype factors as determinants of desmoid tumors in patients with familial adenomatous polyposis. Int J Cancer 2001;95:102-107.
27. Smith TG, Clark SK, Katz DE *et al*. Adrenal masses are associated with familial adenomatous polyposis. Dis Colon Rectum 2000;43:1739-1742.
28. Burt RW, Jasperson KW. *APC*-Associated Polyposis Conditions. 1993.
29. Hamilton SR, Liu B, Parsons RE *et al*. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839-847.
30. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385-398.
31. Vasen HF, Moslein G, Alonso A *et al*. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704-713.
32. Lubbe SJ, Di Bernardo MC, Chandler IP *et al*. Clinical implications of the colorectal cancer risk associated with *MUTYH* mutation. J Clin Oncol 2009;27:3975-3980.
33. Farrington SM, Tenesa A, Barnetson R *et al*. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 2005;77:112-119.
34. Boparai K.S. and others. Hyperplastic Polyps And Sessile Serrated Adenomas As A Phenotypic Expression Of Myh-Associated Polyposis (Map). DOI: 10.1053/j.gastro.2008.09.020 ed. 2008.
35. Knudsen AL, Bisgaard ML, Bulow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Fam Cancer 2003;2:43-55.
36. Soravia C, Berk T, Madlensky L *et al*. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. Am J Hum Genet 1998;62:1290-1301.
37. Spirio L, Otterud B, Stauffer D *et al*. Linkage of a variant or attenuated form of adenomatous polyposis coli to the adenomatous polyposis coli (*APC*) locus. Am J Hum Genet 1992;51:92-100.
38. Burt RW, Leppert MF, Slattery ML *et al*. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 2004;127:444-451.
39. Nielsen M, Hes FJ, Nagengast FM *et al*. Germline mutations in *APC* and *MUTYH* are responsible for the majority of families with attenuated familial adenomatous polyposis (AFAP). Clin Genet 2007;71:427-433.
40. Bonis PA, Trikalinos TA, Chung M *et al*. Hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications. Evid Rep Technol Assess (Full Rep) 2007;1-180.
41. Sankila R, Aaltonen LA, Jarvinen HJ *et al*. Better survival rates in patients with MLH1-associated hereditary colorectal cancer. Gastroenterology 1996;110:682-687.
42. Watson P, Lin KM, Rodriguez-Bigas MA *et al*. Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. Cancer 1998;83:259-266.
43. Barnetson RA, Tenesa A, Farrington SM *et al*. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006;354:2751-2763.
44. Vasen HF, Moslein G, Alonso A *et al*. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 2007;44:353-362.
45. Casey G, Lindor NM, Papadopoulos N *et al*. Conversion analysis for mutation detection in MLH1 and MSH2 in patients with colorectal cancer. JAMA 2005;293:799-809.
46. Lindor NM. Familial colorectal cancer type X: the other half of hereditary nonpolyposis colon cancer syndrome. Surg Oncol Clin N Am 2009;18:637-645.
47. Tomlinson IP, Houlston RS. Peutz-Jeghers syndrome. J Med Genet 1997;34:1007-1011.
48. Jass JR. Colorectal polyposes: From phenotype to diagnosis. Pathol Res Pract 2008;204:431-447.
49. Giardiello FM, Welsh SB, Hamilton SR *et al*. Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 1987;316:1511-1514.
50. Salloch H, Reinacher-Schick A, Schulmann K *et al*. Truncating mutations in Peutz-Jeghers syndrome are associated with more polyps, surgical interventions and cancers. Int J Colorectal Dis 2010;25:97-107.
51. van Lier MG, Wagner A, Mathus-Vliegen EM *et al*. High Cancer Risk in Peutz-Jeghers Syndrome: A Systematic Review and Surveillance Recommendations. Am J Gastroenterol 2010.

52. Aretz S, Stienen D, Uhlhaas S *et al*. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat 2005;26:513-519.
53. Hearle N, Schumacher V, Menko FH *et al*. STK11 status and intussusception risk in Peutz-Jeghers syndrome. J Med Genet 2006;43:e41.
54. McGarrity TJ, Amos C. Peutz-Jeghers syndrome: clinicopathology and molecular alterations. Cell Mol Life Sci 2006;63:2135-2144.
55. Gao H, van Lier MG, Poley JW *et al*. Endoscopic therapy of small-bowel polyps by double-balloon enteroscopy in patients with Peutz-Jeghers syndrome. Gastrointest Endosc 2010;71:768-773.
56. Jass JR, Williams CB, Bussey HJ *et al*. Juvenile polyposis--a precancerous condition. Histopathology 1988;13:619-630.
57. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 1998;5:751-756.
58. Brosens LA, van HA, Hylind LM *et al*. Risk of colorectal cancer in juvenile polyposis. Gut 2007;56:965-967.
59. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 1998;5:751-756.
60. Jarvinen H, Franssila KO. Familial juvenile polyposis coli; increased risk of colorectal cancer. Gut 1984;25:792-800.
61. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 1998;5:751-756.
62. Aretz S, Stienen D, Uhlhaas S *et al*. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet 2007;44:702-709.
63. Calva-Cerqueira D, Chinnathambi S, Pechman B *et al*. The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet 2009;75:79-85.
64. Sweet K, Willis J, Zhou XP *et al*. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA 2005;294:2465-2473.
65. Howe JR, Ringold JC, Hughes JH *et al*. Direct genetic testing for Smad4 mutations in patients at risk for juvenile polyposis. Surgery 1999;126:162-170.
66. Bosserhoff AK, Grussendorf-Conen EI, Rubben A *et al*. Multiple colon carcinomas in a patient with Cowden syndrome. Int J Mol Med 2006;18:643-647.
67. Starink TM. Cowden's disease: analysis of fourteen new cases. J Am Acad Dermatol 1984;11:1127-1141.
68. Pilarski R. Cowden syndrome: a critical review of the clinical literature. J Genet Couns 2009;18:13-27.
69. Eng C. PTEN Hamartoma Tumor Syndrome (PHTS). 1993.
70. Lashner BA, Riddell RH, Winans CS. Ganglioneuromatosis of the colon and extensive glycogenic acanthosis in Cowden's disease. Dig Dis Sci 1986;31:213-216.
71. Eng C. Cowden Syndrome. Journal of Genetic Counseling 1997;Volume 6, Number 2 :181-192.
72. Gorlin RJ, Cohen MM, Jr., Condon LM *et al*. Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet 1992;44:307-314.
73. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982;23:835-842.
74. Paspatis GA, Papanikolaou N, Zois E *et al*. Prevalence of polyps and diverticulosis of the large bowel in the Cretan population. An autopsy study. Int J Colorectal Dis 2001;16:257-261.
75. Williams GT, Arthur JF, Bussey HJ *et al*. Metaplastic polyps and polyposis of the colorectum. Histopathology 1980;4:155-170.
76. Ferrandez A, Samowitz W, Disario JA *et al*. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. Am J Gastroenterol 2004;99:2012-2018.
77. Chow E, Lipton L, Lynch E *et al*. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30-39.

78. Boparai KS, Mathus-Vliegen EM, Koornstra JJ *et al*. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut 2009.
79. Spring KJ, Zhao ZZ, Karamatic R *et al*. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. Gastroenterology 2006;131:1400-1407.
80. Jass JR, Baker K, Zlobec I *et al*. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-131.
81. Rashid A, Houlihan PS, Booker S *et al*. Phenotypic and molecular characteristics of hyperplastic polyposis. Gastroenterology 2000;119:323-332.
82. Lage P, Cravo M, Sousa R *et al*. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. Am J Gastroenterol 2004;99:1779-1784.
83. Minoo P, Baker K, Goswami R *et al*. Extensive DNA methylation in normal colorectal mucosa in hyperplastic polyposis. Gut 2006;55:1467-1474.
84. Yang S, Farraye FA, Mack C *et al*. BRAF and KRAS Mutations in hyperplastic polyps and serrated adenomas of the colorectum: relationship to histology and CpG island methylation status. Am J Surg Pathol 2004;28:1452-1459.
85. Whitelaw SC, Murday VA, Tomlinson IP *et al*. Clinical and molecular features of the hereditary mixed polyposis syndrome. Gastroenterology 1997;112:327-334.
86. Rozen P, Samuel Z, Brazowski E. A prospective study of the clinical, genetic, screening, and pathologic features of a family with hereditary mixed polyposis syndrome. Am J Gastroenterol 2003;98:2317-2320.
87. Cheah PY, Wong YH, Chau YP *et al*. Germline bone morphogenesis protein receptor 1A mutation causes colorectal tumorigenesis in hereditary mixed polyposis syndrome. Am J Gastroenterol 2009;104:3027-3033.
88. Cao X, Eu KW, Kumarasinghe MP *et al*. Mapping of hereditary mixed polyposis syndrome (HMPS) to chromosome 10q23 by genomewide high-density single nucleotide polymorphism (SNP) scan and identification of BMPR1A loss of function. J Med Genet 2006;43:e13.
89. Bulow S, Christensen IJ, Harling H *et al*. Recurrence and survival after mesorectal excision for rectal cancer. Br J Surg 2003;90:974-980.
90. de Jong AE, Hendriks YM, Kleibeuker JH *et al*. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology 2006;130:665-671.