Clinical management of hereditary colorectal cancer syndromes

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Abstract | Hereditary factors are involved in the development of a substantial proportion of all cases of colorectal cancer. Inherited forms of colorectal cancer are usually subdivided into polyposis syndromes characterized by the development of multiple colorectal polyps and nonpolyposis syndromes characterized by the development of few or no polyps. Timely identification of hereditary colorectal cancer syndromes is vital because patient participation in early detection programmes prevents premature death due to cancer. Polyposis syndromes are fairly easy to recognize, but some patients might have characteristics that overlap with other clinically defined syndromes. Comprehensive analysis of the genes known to be associated with polyposis syndromes helps to establish the final diagnosis in these patients. Recognizing Lynch syndrome is more difficult than other polyposis syndromes owing to the absence of pathognomonic features. Most investigators therefore recommend performing systematic molecular analysis of all newly diagnosed colorectal cancer using immunohistochemical methods. The implementation in clinical practice of new high-throughput methods for molecular analysis might further increase the identification of individuals at risk of hereditary colorectal cancer. This Review describes the clinical management of the various hereditary colorectal cancer syndromes and demonstrates the advantage of using a classification based on the underlying gene defects.

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Introduction

Hereditary factors have a role in around 5–15% of all cases of colorectal cancer (CRC).[1] Timely identification of individuals with a genetic predisposition to CRC is imperative as it enables preventative measures such as colonoscopy to be offered. Periodic examination by colonoscopy has been highly effective in reducing CRC-associated mortality in individuals at high risk of CRC.[1,2] Hereditary CRC is usually subdivided into polyposis syndromes, characterized by the development of multiple (usually tens, hundreds or more) colorectal polyps, and nonpolyposis syndromes, characterized by the development of few or no polyps. The various polyposis syndromes are subclassified based on the pathology of the polyps, in combination with other characteristic clinical features. Identification of the genetic defects underlying most hereditary CRC syndromes has been a major step forward in cancer research and has had very important consequences for clinical practice. First, confirmation of the clinical diagnosis and hereditary nature of these syndromes is now possible. Second, people who are or are not carriers of genetic mutations can now be distinguished and offered presymptomatic diagnosis and prevention if relevant. Third, syndromes can be classified more precisely than previously (Box 1), with targeted surveillance and treatment guided by the underlying genetic defect. Finally, clinically-defined syndromes without underlying genetic defects can be differentiated; these seem to have a different natural history and thus require a different management approach. This Review describes the clinical management of the various hereditary CRC syndromes and demonstrates the advantage of using a classification system based on the underlying gene defects.

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Management of polyposis syndromes

Adenomatous polyposis

APC polyposis

The protein product of the *APC* gene is involved in controlling the Wnt signalling pathway. *APC* mutations cause an accumulation of β-catenin, which then leads to the transcriptional activation of a variety of genes and oncogenes, including *c-Myc* (a transcription factor that activates several genes controlling cell growth and division).[3] *APC* polyposis (also known as familial adenomatous polyposis [FAP]) is an inherited autosomal dominant syndrome characterized by the development of hundreds of colorectal adenomas in the second and third decade of life.[3] If patients are not treated in a timely manner, almost all will develop CRC. The severity of polyposis is associated with the mutation site in the *APC* gene; mutations located at either end of the gene or in exon nine are associated with a mild polyposis phenotype (known as attenuated FAP).[4] Fundic gland polyps and adenomas in the duodenum are also commonly found in patients with FAP (duodenal adenoma >80%), but the risk of developing duodenal cancer is substantially lower (<10–15%) than the risk of CRC (>80%) in untreated patients.[5] In addition,

Key points

- Timely identification of hereditary colorectal cancer syndromes might prevent early death due to cancer
- Systematic analysis of all newly diagnosed colorectal cancer for molecular features of Lynch syndrome will improve the identification of the syndrome
- Comprehensive analysis of the genes known to be associated with polyposis syndromes facilitates making an appropriate diagnosis
- Classification of hereditary colorectal cancer syndromes according to the underlying gene defect enables targeted surveillance and treatment
- Inclusion of the underlying gene defect in disease terminology and diagnosis ensures appropriate management

Box 1 | Hereditary CRC syndromes based on mutations

Polyposis syndromes

Adenomatous polyposis
- *APC* polyposis (classical familial adenomatous polyposis)
- *MUTYH* polyposis
- *POLE or POLD1* polyposis
- Adenomatous polyposis associated with biallelic MMR-mutations (CMMRD[1])
- Adenomatous polyposis without gene defect (clinical adenomatous polyposis)

Polyposis with variable histology
- *STK11* polyposis (as part of Peutz–Jeghers syndrome)
- *SMAD4 or BMPRA1* polyposis (juvenile polyposis)
- *PTEN* polyposis (as part of *PTEN*-hamartoma syndrome)
- *GREM1* polyposis (hereditary mixed polyposis syndrome)

Other polyposis without known gene defect
- Serrated polyposis

Nonpolyposis colorectal cancer syndromes

Lynch syndrome
- *MLH1*-Lynch syndrome
- *MSH2*-Lynch syndrome
- *EPCAM*-Lynch syndrome*
- *MSH6*-Lynch syndrome
- *PMS2*-Lynch syndrome

Probable Lynch syndrome‡

Familial colorectal cancer§

*Deletion of 3′ end of *EPCAM* with hypermethylation of the promoter of *MSH2* gene. ‡Colorectal cancer (or other tumours associated with Lynch syndrome) with microsatellite instability, mutation analysis negative and exclusion of *MLH1* methylation and biallelic somatic mutations. §Familial clustering of CRC(s) without microsatellite instability. Abbreviations: CMMRD, constitutional mismatch repair deficiency; CRC, colorectal cancer; MMR, mismatch repair.

patients with FAP have a slightly increased risk of cancers at other sites, including the brain, thyroid and liver (hepatoblastoma). Other features commonly found in patients with *APC* polyposis include abdominal desmoids, congenital hypertrophy of the retinal pigment epithelium, osteomas, dental abnormalities, epidermoid cysts and adrenal masses.[6]

The surveillance programme for *APC* polyposis consists of sigmoidoscopy (or colonoscopy under general anaesthesia in children) starting from the age of 10–15 years (colonoscopy from age 18 years in attenuated FAP), with an interval of 1–2 years depending on the findings (Table 1).[2] Periodic examination of the duodenum should commence between the ages of 25 and 30 years. The severity of the adenomatosis can be assessed using a scoring system that is used to determine intervals between examinations.[2]

The surgical treatment for colorectal polyposis is total colectomy, or proctocolectomy if patients have multiple adenomas in the rectum and/or if the patient has a genotype that is associated with severe disease.[3] The timing of colorectal surgery depends on the number and size of adenomas and the presence of polyps with high-grade dysplasia. In patients with attenuated FAP who have only a few adenomas (Figure 1), the preferred treatment is endoscopic polypectomy instead of surgery.[4] In some patients with *APC* polyposis, treatment with sulindac can be used to reduce the number of adenomas and postpone surgery.[5] The preferred treatment for duodenal polyps is endoscopic removal of adenomas by an experienced gastroenterologist. Celecoxib has been reported to reduce the number of polyps but the effect is small (~15% reduction in the number of polyps).[6] Severe cases might show development of large, multiple sessile duodenal polyps with a high degree of dysplasia that cannot be removed endoscopically, even by an expert gastroenterologist; in this instance, surgical resection of the duodenum is advised.[2]

Following the successful worldwide establishment of polyposis registries and the implementation of surveillance programmes, mortality due to CRC in *APC* polyposis has been substantially reduced.[7] Other neoplasms, including desmoid tumours and duodenal cancer, are now the main causes of death in patients with *APC* polyposis.[8] Desmoid tumours are histologically benign tumours, but they can have an unpredictable and sometimes aggressive growth pattern, leading to serious morbidity or even mortality by local infiltration into surrounding vital structures.[9] 10–15% of patients with polyposis have desmoid tumours, which mainly occur in the abdomen.[10] The initial treatment of desmoid tumours consists of medical treatment (sulindac with either tamoxifen or toremifene).[9] Surgery is recommended in patients with extra-abdominal desmoid tumours. Most clinicians express reluctance regarding the surgical removal of intra-abdominal desmoid tumours because experience indicates that abdominal surgery might enhance the growth of desmoid tumours.[11]

MUTYH polyposis

MUTYH polyposis (commonly known as MUTYH-associated polyposis [MAP]) is a recessively inherited syndrome characterized by the development of multiple colorectal adenomas (usually <100) in the third and fourth decade of life.[12] The underlying causative gene, *MUTYH*, is one of the base excision repair genes, which are involved in the repair of genetic mutations caused by reactive oxygen species and DNA damage due to methylation, deamination and hydroxylation.[13]

Patients with *MUTYH* polyposis have a 60–70% risk of developing CRC[12] and some patients might develop duodenal adenomas or duodenal cancer. A small proportion of patients might fulfil the criteria for serrated polyposis if adenomas and serrated polyps are found in the colon.[14] Studies have also demonstrated a slightly increased risk of ovarian, bladder and skin (sebaceous tumours) cancer in patients with *MUTYH* polyposis.[15] Endometrial cancer

Table 1 | Surveillance recommendations*

Study	Syndrome	Gastrointestinal tract surveillance	Surveillance at other sites‡
Adenomatous polyposis			
Vasen *et al.* (2008),[2] NNCN guidelines[4]	*APC* polyposis	Sigmoid or colonoscopy every 1–2 years§ from age 10–15 years; upper gastrointestinal endoscopy every 6 months to 4–5 years§ from age 25–30 years; postoperative follow-up of the rectum, pouch and ileostomy every 6–12 months§	Thyroid, liver (hepatoblastoma)
Vasen *et al.* (2008),[2] NNCN guidelines[4]	*MUTYH* polyposis	Colonoscopy every 1–2 years§ from age 18–30 years; upper gastrointestinal endoscopy every 6 months to 4–5 years§ from age 25–35 years; postoperative follow-up of rectum, pouch and ileostomy every 6–12 months§	NA
Vasen *et al.* (2014)[22]	Adenomatous polyposis associated with biallelic MMR mutations (CMMRD)	Colonoscopy every 1–2 years§ from age 8; upper gastrointestinal endoscopy and VCE every year from age 10 years	Brain, non-Hodgkin lymphoma, endometrium, urinary tract
NNCN guidelines,[4] Hes *et al.* (2014)[23]	Adenomatous polyposis without gene defects	Initial colonoscopy at an early age (15–20 years) and additional colonoscopic surveillance every 5 years from 30 years	NA
Polyposis with variable histology			
NNCN guidelines,[4] Beggs *et al.* (2010)[24]	*STK11* polyposis (Peutz–Jeghers syndrome)	Colonoscopy or upper gastrointestinal endoscopy at age 8–10 years; if no polyps detected repeat at age 18 years; if polyps detected, colonoscopy or upper gastrointestinal endoscopy every 3 years; VCE or MRI-enteroclysis at age 10 years and 18 years. If age >18 years, VCE or MRI-enteroclysis every 2–3 years§	Breast, pancreas, endometrium, cervix, ovaries
NNCN guidelines,[4] Brosens *et al.* (2007)[31]	*SMAD4* or *BMPRA1* polyposis (juvenile polyposis)	Colonoscopy and upper gastrointestinal endoscopy every 1–3 years§ from age 15 years	*SMAD4*-assocated polyposis: vascular lesions in lung, brain and liver
Nieuwenhuis *et al.* (2014),[35] Tan *et al.* (2012),[36] Bubien *et al.* (2013),[37] Nieuwenhuis *et al.* (2012)[38]	*PTEN* polyposis	Colonoscopy every 5 years§ from age 40–45 years	Breast, thyroid, endometrium, kidney‖
Other polyposis without known gene defect			
NNCN guidelines[4]	Serrated polyposis	Colonoscopy every 1–3 years§ from age 45 years	NA
Nonpolyposis CRC			
NNCN guidelines,[4] Vasen *et al.* (2013)[51]	*MLH1*-Lynch syndrome and *MSH2*-Lynch syndrome	Colonoscopy every 1–2 years from age 20–25 years	Endometrium (ovaries), urinary tract
NNCN guidelines,[4] Vasen *et al.* (2013)[51]	*EPCAM*-Lynch syndrome	Colonoscopy every 1–2 years from age 20–25 years	Endometrium (ovaries)
NNCN guidelines,[4] Vasen *et al.* (2013)[51]	*MSH6*-Lynch syndrome and *PMS2*-Lynch syndrome	Colonoscopy every 1–2 years from age 25–30 years	Endometrium (ovaries)
Familial CRC			
Mesher *et al.* (2014)[71]	Familial CRC	Colonoscopy every 5 years from age 45 years	NA

*Almost all recommendations are based on expert opinion. ‡Preferably assessed in a research setting. §Depending on polyp burden. ‖Only slightly increased risk. Abbreviations: CMMRD, constitutional mismatch repair deficiency; CRC, colorectal cancer; FAP, familial adenomatous polyposis; MMR, mismatch repair; NA, not applicable; NNCN, national comprehensive cancer network; VCE, video capsule endoscopy.

has also been reported in *MUTYH* polyposis, but the incidence was not increased substantially compared with healthy individuals.[15] Some clinical features are observed in both FAP and *MUTYH* polyposis, such as osteomas, fundic gland polyposis and congenital hypertrophy of the retinal pigment epithelium; however, desmoid tumours do not seem to be a component of the tumour spectrum observed in *MUTYH* polyposis. Recommendations for the surveillance and management of *MUTYH* polyposis are largely similar to those for *APC* polyposis with a mild phenotype (that is, colonoscopy from age 18, with an interval of 1–2 years depending on the findings; Table 1).[2] Several studies have reported a slightly increased risk of developing CRC in people with monoallelic *MUTYH*

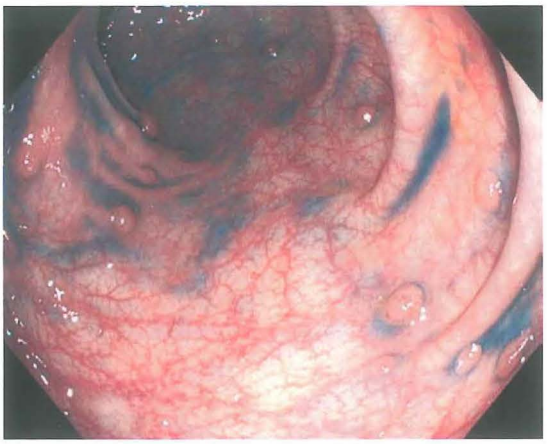

Figure 1 | APC polyposis syndrome. Colonoscopy in a 26-year-old patient with attenuated polyposis.

mutations;[16] these individuals should be screened in the same way as individuals with an average risk of CRC.[4]

POLE and POLD1 polyposis

Germline mutations have been identified in the *POLE* and *POLD1* genes in families with several cases of multiple adenomas and early-onset CRC.[17] The *POLE* gene encodes a protein that carries out leading strand synthesis during DNA replication. The POLE exonuclease domain also has a proofreading capacity that is essential for the maintenance of replication fidelity. *POLD1* encodes a protein that performs a similar function for the lagging strand and is also thought to participate in the mismatch and base excision repair pathways.[17]

A *POLE* variant, p.L424V, was genotyped in a validation phase sample of 3,805 patients with CRC. The cohort was enriched for patients with a family history of colorectal tumours, multiple adenomas and early-onset disease.[17] The variant, which impairs proofreading, was found in 12 cases (0.3%) but was absent in healthy controls. In another series of patients with familial or early-onset CRC and polyposis, a *POLE* p.L424V mutation was identified in one of 858 patients (0.1%).[18] The pedigrees of the individuals were compatible with a dominantly inherited trait and were characterized by early-onset CRC (age at diagnosis of CRC varied from 25 years to 65 years), multiple CRC and the presence of multiple adenomas. Other pathogenic *POLE* and *POLD1* mutations cause similar phenotypes.[17–19] Families with *POLE* or *POLD1* mutations have an increased risk of endometrial cancer and other tumour types.[17–19] On the basis of these findings, colonoscopy at 3 year intervals starting from an age of 30–35 years is recommended, but firm guidance is not yet possible because to date, published evidence is from a few families and management might also depend on the family's tumour phenotype.

Constitutional mismatch repair deficiency

An increasing number of patients have been found to have biallelic mutations in genes involved in mismatch repair (MMR) in which the MMR defects are inherited from both parents. MMR gene defects result in a syndrome with recessive inheritance, referred to as constitutional mismatch repair deficiency (CMMRD). Biallelic mutations are more often observed in *PMS2* and *MSH6* than in the other MMR genes. The clinical hallmark of CMMRD is the presence of multiple café au lait spots, which might help to identify patients with the deficiency.

The spectrum of cancers observed in patients with CMMRD differs from the spectrum found in patients with Lynch syndrome, as about half of patients develop brain tumours, around half develop digestive tract cancers (40% develop CRC and 12% develop small bowel cancer) and one-third develop haematological malignancies (mainly non-Hodgkin lymphoma).[20,21] Brain tumours and haematological malignancies are mainly diagnosed in the first decade of life;[17,20,21] CRC and small bowel cancer occur in the second and third decades of life[17,20,21] and endometrial cancers and urinary tract cancers are diagnosed in young adults (>20 years) with CMMRD.[20,21] Studies on the colonic phenotype in patients with CRC have shown that multiple adenomas, usually numbering between 10 and 100, are found in >50% of patients. Surveillance recommendations are summarized in Table 1.[22]

Adenomatous polyposis without known gene defect

In a substantial proportion of patients with polyposis, an underlying genetic defect cannot be identified. In a study on a large series of patients with 10 to >100 polyps and no defect in *APC, MUTYH, POLD1* or *POLE*, the authors evaluated whether single nucleotide polymorphisms (SNPs) that are associated with CRC have a role in the development of polyposis.[23] Two SNPs (rs3802842 and rs4779584) were found to be associated with polyposis. The family history of patients showed that only a very small number (1%) had a positive family history of polyposis.[24] This finding suggests that adenomatous polyposis without an underlying *APC, MUTYH, POLD1* or *POLE* gene defect is seldom an inherited disease. An additional and important observation was that half of the first-degree relatives of patients with polyposis were found to have CRC (mean age 60 years). Therefore, the authors advised performing an initial colonoscopy to exclude polyposis at an early age (15–20 years) and additional surveillance by colonoscopy starting from the age of 30 years, repeated at intervals of 5 years in first-degree relatives (Table 1).

Polyposis with variable histology

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is an autosomal dominant condition typified by the development of characteristic polyps throughout the gastrointestinal tract and by the presence of mucocutaneous pigmentation, usually around and inside the mouth and perianal region. Peutz–Jeghers polyps are found most frequently in the small bowel and colon, and less often in the stomach and extraintestinal sites comprising the bronchus, gall bladder, nasal passages and urinary tract. Cystic gland dilatation and arborizing smooth muscle

are characteristic histological features of the polyps (Figure 2). Signs and symptoms that might occur include gastrointestinal bleeding, anaemia and abdominal pain due to intussusception, obstruction or infarction.[24]

Peutz–Jeghers syndrome is due to germline mutations in the *STK11* gene.[24] The *STK11* gene is involved in various processes such as cell metabolism, cell polarity, apoptosis and DNA-damage responses. STK11 acts as an upstream regulator of AMP-activated protein kinase (AMPK) and as a negative regulator of the mammalian target of rapamycin (mTOR) pathway.[24]

Treatment consists of endoscopic polypectomy during upper gastrointestinal endoscopy and double balloon enteroscopy if large polyps are detected by video capsule endoscopy or MRI-enteroclysis. Endoscopic polypectomy is performed to prevent small bowel intussusception or obstruction in childhood and adolescence, and reduce cancer risk at a more advanced age.[24] As the malignant potential of Peutz–Jeghers polyps is unknown, it is not clear whether polypectomy alters the risk of developing cancer; however, the risk of intussusception and obstruction is reduced by removing small bowel polyps.[25]

Many studies have demonstrated that patients with *STK11*-associated polyposis have an increased risk of developing a variety of cancers, including gastrointestinal (57% by the age of 70 years), breast (45% by age 70 years), gynaecological (18% by age 70 years) and pancreatic (10% by age 70 years)[26] Female patients are at risk of sex cord tumours with annular tubules (a benign neoplasm of the ovaries) and adenoma malignum of the cervix (a rare aggressive cancer).[24] Male patients occasionally develop large calcifying sertoli cell tumours of the testes, which secrete oestrogen and can lead to gynaecomastia, advanced skeletal age and short stature.[24,27] As such, an extensive surveillance programme is recommended and detailed in Table 1. Several agents have shown promise for the reduction of the polyp burden in *STK11*-associated polyposis (for example rapamycin, everolimus and metformin), although none are in clinical use.[24]

Juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant inherited condition characterized by the development of so-called juvenile polyps (Figure 3).[28,29] The syndrome is caused by mutations in *SMAD4* or *BMPR1A*, which are involved in the bone morphogenetic protein (BMP)–TGF-β pathway.[30] Juvenile polyps have a distinctive histology characterized by an abundance of oedematous lamina propria with inflammatory cells and cystically dilated glands lined by cuboidal to columnar epithelium with reactive changes.[28,29] Most polyps occur in the colorectum but they are also found in the upper digestive tract.[28,29] Signs and symptoms that might occur include ferriprive anaemia and abdominal complaints. Juvenile polyposis is diagnosed clinically if a patient has ≥5 juvenile polyps in the colorectum, juvenile polyps throughout the digestive tract or any number of these polyps if the patient has a positive family history for juvenile polyposis.[28,29] The lifetime risk of CRC is ~40% and ~10% for both gastric and small bowel cancer.[31]

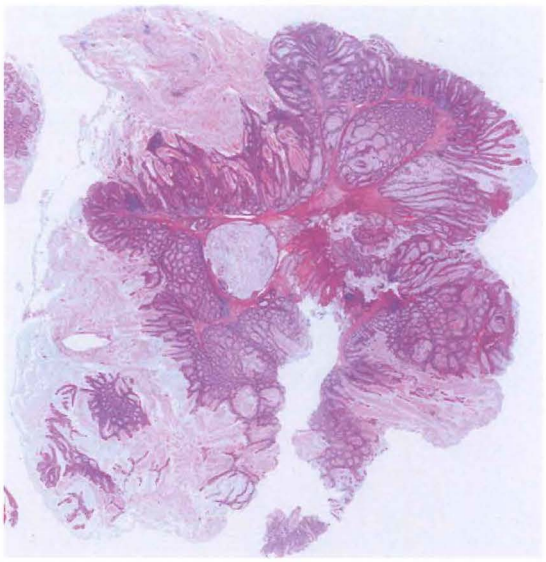

Figure 2 | Peutz–Jeghers polyp with arborizing smooth muscle separating the glands into lobes. x10 magnification. Image courtesy of Prof Hans Morreau and Dr Marcus Breemer www.hereditarypathology.org.

Mutations in the *SMAD4* and *BMPR1A* genes each account for about 25% of cases of JPS.[28,29] Some evidence exists that patients with a *SMAD4* mutation have a more aggressive phenotype and have a higher frequency of gastric polyps and gastric cancer compared with patients with a *BMPR1A* mutation.[32] Patients with *SMAD4* mutations might also develop hereditary haemorrhagic telangiectasia (also known as Rendu–Osler-Weber syndrome).[33]

Recommendations for surveillance include colonoscopy and upper gastrointestinal endoscopy starting from the age of 15 years.[4,31,34] Colonoscopy intervals are determined by the presence of polyps and vary from annual follow-up if polyps are present, to every 3 years in those patients without a polyp.[28,29] All polyps should be endoscopically removed. In patients with JPS who have a germline *SMAD4* mutation, screening for signs of hereditary haemorrhagic telangiectasia should be considered and should include chest radiography for arteriovenous malformations, MRI of the brain and liver ultrasonography.

PTEN hamartoma syndrome

PTEN hamartoma syndrome is an inherited multiple hamartoma syndrome associated with a high risk of developing cancer in various organs.[28] *PTEN* hamartoma syndrome is the collective term for several clinical syndromes with overlapping characteristics caused by mutations in *PTEN*, which include Cowden disease, Lhermitte–Duclos disease (a benign tumour known as cerebellar gangliocytoma), and Bannayan–Riley–Ruvalcaba syndrome (also known as Bannayan–Zonana syndrome). *PTEN* has a variety of functions, including inhibition of the PI3K/Akt signalling pathway, maintaining genomic stability, DNA repair, stem cell self-renewal, cellular senescence and cell migration and metastasis. Individuals who have a *PTEN* mutation have an increased risk of developing breast,

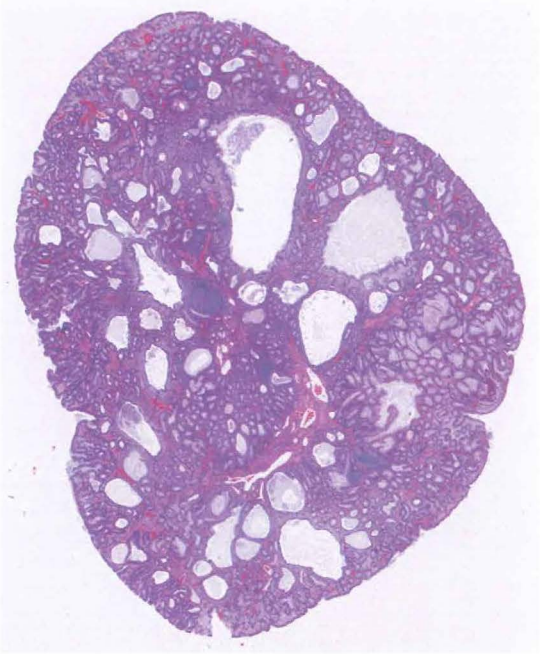

Figure 3 | Juvenile polyp in a patient with a mutation in *BMPRA1*. The polyp shows cystically dilated glands and proliferated small glands without dysplasia. x10 magnification. Image courtesy of Prof Hans Morreau and Dr Marcus Breemer www.hereditarypathology.org.

thyroid, endometrium, kidney and colorectal cancer, as well as Lhermite-Duclos disease.[35–37]

Gastrointestinal polyps, most often hamartomatous, can be found in one-third of patients with *PTEN* hamartoma syndrome.[28] The malignant potential of these polyps is unknown. Nonetheless, the risk of developing CRC is increased by a factor of three in patients with this syndrome.[38] Other benign manifestations of the syndrome include trichilemmomas, oral mucosal papillomatosis, acral keratoses, palmoplantar keratoses, gingival hyperplasia and fibromas in the breast.

Colonoscopic surveillance is recommended from the age of ~40–45 years, with intervals of 5 years depending on the findings.[38] The recommendations for surveillance of the other organs affected by the syndrome are shown in Table 1.[36,37] Studies in mice with a *PTEN* mutation suggest that blockade of mTOR with sirolimus and its analogues might represent a suitable therapeutic option for patients with Cowden disease.[39] Future studies should evaluate the effectiveness of mTOR inhibitors in the clinical setting.

GREM1 mixed polyposis syndrome

GREM1 mixed polyposis syndrome (also known as hereditary mixed polyposis syndrome [HMPS]) is a rare autosomal dominant inherited disease characterized by the development of a variety of polyps, including adenomas, hyperplastic or serrated polyps, juvenile polyps, polyps with mixed pathology and CRC.[40] To date, no report of extra-colonic disease has been made. Mutations in *BMPR1A* have been reported in families with *GREM1* mixed polyposis syndrome, but this finding probably resulted from a degree of phenotypic overlap between HMPS and JPS.[41] A 2012 study in Ashkenazi families suggests that *GREM1* mixed polyposis syndrome results from a duplication and overexpression of GREM1, a gene that encodes a secreted BMP antagonist.[40]

Serrated polyposis

Over the past decade, an increasing number of reports have described patients with hyperplastic polyposis, currently referred to as serrated polyposis. The polyps observed in these patients include hyperplastic polyps, traditional serrated adenomas, sessile serrated polyps and mixed polyps.[42] According to diagnostic criteria established by the WHO, at least five serrated polyps proximal to the sigmoid colon, two of which are >1 cm, or 20 serrated polyps throughout the colon independent of size should be present for a positive diagnosis of serrated polyposis;[43] however, these criteria are likely to evolve in the coming years. An underlying genetic defect responsible for serrated polyposis has not been found.

Serrated polyposis is found in a small minority (~5%) of family members of affected patients, which suggests that only a small number of patients have a heritable syndrome.[44] On the other hand, cohort studies have demonstrated an approximately fivefold increased incidence of CRC in first-degree relatives of patients with serrated polyposis compared with the general population.[45,46] Recommendations for surveillance in patients with serrated polyposis include colonoscopy at 1–3 year intervals—depending on the number of polyps. All polyps >3 mm should be removed. Colonoscopy should be performed in first-degree relatives at least once at an early age to exclude the presence of polyposis.[47] Colonoscopy is then advised at intervals of 5 years from the age of 45 years in first-degree relatives, because of the increased risk of developing CRC at an advanced age.

Management of hereditary nonpolyposis CRC

Lynch syndrome

Lynch syndrome is an autosomal dominant inherited condition characterized by the development of early-onset CRC, endometrial, urinary tract, gastric, small bowel and other cancers.[48] The syndrome is caused by a defect in one of the MMR genes: *MLH1*; *MSH2* (including *EPCAM*-deletion mediated *MSH2* hypermethylation); *MSH6*; and *PMS2*. MMR genes repair errors that occur during DNA replication before cell division. Deficiency in DNA replication repair leads to microsatellite instability (MSI) in tumours, a hallmark of the syndrome.[49]

CRC in patients with Lynch syndrome is typified by accelerated carcinogenesis, probably owing to the secondary involvement of oncogenes and tumour suppressor genes that are mutated as a result of MMR deficiency. Sporadic CRC usually takes >10 years to develop, whereas in Lynch syndrome CRCs have been reported <2 years after a 'clean' colonoscopy (Figure 4).[50] As such, intensive colonoscopic surveillance starting at the age of 25 years is recommended, with intervals of no more than 2 years.[50] Surveillance for other cancers is also recommended, but the effectiveness of the recommended protocols remains unproven.[51] By reason of the high risk of developing a

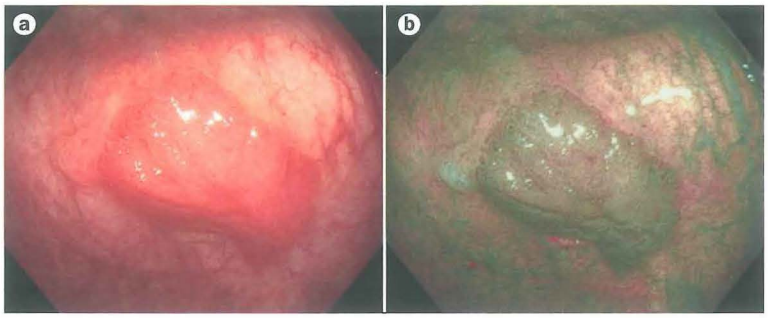

Figure 4 | Adenomatous polyp in a patient with MSH2-Lynch syndrome. Corresponding images of **a** | white light colonoscopy and **b** | narrow-band imaging of a sessile adenoma with high-grade dysplasia 1 year after a normal colonoscopy. Image courtesy of Dr Alexandra Langers and Drs Kristin Robbers.

second CRC, the option of subtotal colectomy in a young patient with CRC should be discussed.[52] Prophylactic hysterectomy and bilateral oophorectomy should be offered to individuals with a mutation in *MSH2*, *MLH1* and *MSH6* with a complete family history.

The CAPP2 studies have reported on the effect of aspirin (600 mg daily) on adenoma and carcinoma development in Lynch syndrome.[53,54] Although in the first study aspirin did not reduce the risk of colorectal adenoma or carcinoma over a treatment duration of 29 months, in the second follow-up study, fewer participants who used aspirin developed CRC compared with those who did not take aspirin (18 versus 30 participants).[53,54] Secondary analysis also revealed fewer extra-colonic cancers associated with Lynch syndrome in patients on aspirin for at least 2 years (incident RR 0.42; 95% CI 0.25–0.72). Although aspirin is associated with gastrointestinal bleeding and intracranial bleeding, no differences in adverse effects between the aspirin group and control group were observed. The optimal dose is still unknown and will need to be determined by further randomized studies, such as the CAPP3 trial.

Over the past decade, research on the risk of cancer associated with Lynch syndrome has indicated that the underlying gene defect determines the risk of developing various cancers, including the age of disease onset.[55–59] Differences in the risk of developing a specific cancer and the age of onset between the various MMR gene defects warrants specific recommendations for surveillance, as described in the following sections. A new system of terminology for Lynch syndrome has been created to reflect the underlying genetic mutation.

MLH1-Lynch syndrome

Together with *MSH2*, *MLH1* is one of the most frequently mutated MMR genes. Individuals with an *MLH1* mutation have an increased risk of the whole spectrum of cancers associated with Lynch syndrome. The risk of developing CRC is about 50% by the age of 70 years and the mean age of diagnosis is ~45 years.[55] The risk of developing endometrial cancer is ~20–50% and the risk of urinary tract cancer in male patients is 4–16%.[60] A small but substantially increased risk of developing breast cancer has been reported.[59,61] Surveillance can be considered for cancers of the urinary tract, endometrium and ovaries (Table 1) but because the effectiveness is still unknown, surveillance should only be performed in a research setting.[51] If further studies confirm an increased risk of breast cancer, the surveillance programme could be extended with regular mammography.

MSH2-Lynch syndrome

The risk of developing CRC and the age of onset of CRC in patients with *MSH2* mutations are similar to those with *MLH1* mutations. The risk of developing endometrial cancer is also similar. However, patients with *MSH2* mutations have a moderately increased risk of developing cancers across the whole spectrum of tumours associated with Lynch syndrome.[55] Especially prominent is the high risk of urinary tract cancer in both male and female patients. Reports also suggest that these patients have an increased risk of prostate cancer.[62] Surveillance recommendations are similar to those for patients with *MLH1* mutations (Table 1).

EPCAM-Lynch syndrome

Loss of MSH2 expression is usually caused by a defect in *MSH2*, but in about 10% of patients it is because of a deletion of the 3' end of the *EPCAM* gene. *EPCAM* is immediately upstream of *MSH2* and partial *EPCAM* deletion causes Lynch syndrome through hypermethylation of the *MSH2* promoter.[63–65] The risk of CRC in patients with *EPCAM* mutations and *MSH2* mutations is similar. However, the risk reported for endometrial cancer was only 12% by the age of 70 years for patients with EPCAM mutations (compared with 20–50% in those with *MSH2* mutations).[66]

MSH6-Lynch syndrome

An increasing number of people with *MSH6* mutations have been identified over the past decade.[67] Patients with mutations in *MSH6* carry a substantially lower risk of CRC (10% in female patients and 22% in male patients) and their age at onset of CRC is about 10 years later than that in people with *MLH1* and *MSH2* mutations.[58] Some reports have suggested that female patients with *MSH6* mutations have a higher risk of endometrial cancer than those with other MMR gene mutations;[68] however, the largest study to date (including 113 families) reported a risk of 26% by the age of 70 years, which is comparable to that associated with *MLH1* and *MSH2* mutations (see earlier).[58] The risk of developing other cancers associated with Lynch syndrome is much lower in people with *MSH6* mutations (3% for male patients and 11% for female patients at the age of 70 years) compared with patients who have *MLH1* and *MSH2* mutations.[59] Surveillance examinations might therefore be restricted to the colon and endometrium. In view of the late onset of CRC in these patients, delaying the start of colonoscopic surveillance could be considered (for example, from the age of 25–30 years onwards).[4]

PMS2-Lynch syndrome

The detection of *PMS2* mutations was initially complicated by the presence of pseudogenes and gene conversion. Once

this issue was resolved, increasing numbers of people have been identified as having *PMS2* mutations. Only a single study has reported on the risk of developing cancer in relation to *PMS2* mutations and this report suggested that the risk of developing CRC, endometrial cancer and other cancers is quite low (~20% and ~15% for CRC and endometrial cancer, respectively) and at a level approximately similar to that in people with *MSH6* mutations.[57] In 2014, a large European cohort study including 98 families confirmed these findings (risk of CRC risk was 19% and risk of endometrial cancer was 12%).[56] Recommendations for colonoscopic surveillance are the same as those recommended for people with *MSH6* mutations (Table 1).

Probable Lynch syndrome

In ~25% of patients with a tumour showing molecular genetic evidence of Lynch syndrome (including loss of expression of one or two of the MMR proteins, the presence of MSI and absence of somatic *MLH1* methylation), an underlying gene mutation cannot be identified.[69] Almost half of these patients have biallelic somatic mutations in the MMR genes (*MLH1* and *MSH2*) that are responsible for development of their sporadic cancer.[69] The remaining patients probably have an unidentified underlying MMR defect. Recommendations for surveillance and management of these patients and their first-degree relatives are similar to those with proven MMR mutations (Table 1).

Familial CRC

Families that match with the Amsterdam criteria type I (that is all three of the following: three relatives with CRC in two generations; one of whom is a first-degree relative of either of the other two; and one of the patients was diagnosed at <50 years of age) have been reported in which there is no evidence for MSI or loss of expression of the MMR genes in the CRC observed.[70] People with CRC from these families are referred to as having type X familial CRC or, more simply, familial CRC. The typical cancers associated with Lynch syndrome, such as endometrial cancer and urinary tract cancer, are generally absent and the risk of relatives developing CRC seems to be much lower than in families with Lynch syndrome.[70] A variant of the criteria exists in families that meet the Amsterdam criteria type I except for the age criterion (that is, all CRCs are diagnosed at >50 years of age); these families are usually described as 'late-onset familial clustering of CRC'. Many of these families might represent chance clusters of disease, perhaps with modest genetic and/or environmental influences in some. The recommended surveillance protocol consists of colonoscopy once every 5 years, starting from the age of 45 years.[71,72]

Conclusions

Timely identification of hereditary CRC syndromes is vital because participation in early detection programmes could prevent premature death due to cancer. Syndromes associated with the development of multiple colorectal polyps are fairly easy to recognize. Pathological examination of the polyps, in combination with the presence of specific features associated with the various polyposis syndromes, usually leads to an accurate diagnosis. However, some patients with polyposis might have multiple polyps with variable histology and might show overlap between clinically defined syndromes such as hereditary mixed polyposis syndrome, juvenile polyposis and serrated polyposis. In such situations, comprehensive analysis of the genes known to be associated with polyposis syndromes (such as *APC*, *MUTYH*, *SMAD4*, *BMPR1A*, *GREM1*, *STK11*, *PTEN*, *POLE* and *POLD1*) helps to establish the final diagnosis.

Recognizing Lynch syndrome is more difficult than polyposis syndromes owing to the absence of pathognomonic features. According to studies by Finnish and US investigators, the frequency of people with an MMR gene defect is estimated at 1 in 500–1,000 in the general population.[73] However, fewer than half of these individuals are currently identified. Over the past 25 years various criteria,[74–76] guidelines[77–79] and predictive models[80,81] have been proposed to help improve the identification of families with Lynch syndrome, but they have not made enough of an improvement. All of these tools to improve identification assume that an adequate family history has been taken, despite the fact that it is well known that family history is often neglected in general practice.[82] As a consequence, most investigators recommend performing systematic molecular analysis of all newly diagnosed CRC and endometrial cancer using immunohistochemical methods or MSI analysis.[51,83,84] Several studies have now shown that this approach leads to the identification of substantial numbers of patients with Lynch syndrome.[51]

Finally, the implementation in clinical practice of new and very effective (and cost-effective) high-throughput methods for molecular analysis, using panels of hereditary (CRC) cancer-associated genes or whole-exome sequencing, might further increase the identification of individuals at risk of hereditary CRC.

Since the discovery of the underlying gene defects for most hereditary CRC syndromes over the past few decades, knowledge of the phenotypes of conditions associated with specific gene defects has increased substantially. This knowledge can now be implemented in clinical practice, and the classification of hereditary CRC syndromes by underlying gene defect (Box 1) will facilitate this process. For example, patients with a known MMR gene defect are currently referred to as having Lynch syndrome; however, because the cancer risk and the recommendations for surveillance differ substantially for patients with different MMR gene defects, we advise the inclusion of the underlying gene defect in disease terminology and diagnosis, such as *MLH1*-Lynch syndrome. In addition, including the underlying gene defect in the polyposis syndrome terminology facilitates appropriate management. Juvenile polyposis, for example, is caused by a defect in either *BMPR1A* or *SMAD4*. Patients with *SMAD4*-associated juvenile polyposis, in contrast to those with *BMPR1A*-associated juvenile polyposis, might also develop hereditary haemorrhagic telangiectasias, which requires specific diagnostic examination and management. In conclusion, improved identification

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Author contributions

H.F.A.V. researched data and wrote the manuscript. I.T. and A.C. substantially contributed to discussion of content, and reviewed and edited the manuscript before submission.