

# Hereditary colorectal cancer

## What you need to know

### Key points

- Hereditary colorectal cancer (CRC) syndromes are uncommon but their diagnoses allow risk management to prevent CRC and other malignancies.
- Family history and personal history are essential for clinical diagnosis.
- Medicare and private health insurance do not fund genetic testing for most hereditary cancer syndromes.
- Diagnostic genetic testing has limitations, and is usually reserved for patients meeting clinical diagnostic criteria.
- Identification of a deleterious gene mutation in a family allows 'predictive testing' (which can determine family members with/without the mutation) and also opens up reproductive options (e.g. pre-implantation genetic diagnosis).
- **eviQ Cancer Treatments Online (<http://www.eviq.org.au>) has guidelines on referral, genetic testing and risk management, and information on familial cancer clinics in Australia.**

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Recognising hereditary colorectal cancer syndromes is important as there are implications for both patients and their families. General practitioners are often the first point of patient contact, thereby playing a pivotal role in providing information and guidance. A balance between risk awareness and understanding of the benefits versus limitations of genetic testing is important.

Colorectal cancer (CRC) is the second most common malignancy in both men and women in Australia, with an incidence of approximately one in 10 for men and one in 15 for women.<sup>1</sup> It represents the second most common cause of cancer deaths after lung cancer.<sup>1</sup>

CRC can be sporadic, familial or hereditary, with sporadic CRC constituting the majority of cases (65 to 85%). Approximately 20 to 30% of CRC is familial, with aetiology largely unknown and thought to be multifactorial, involving complex interactions between genetic susceptibility and environmental

factors.<sup>2</sup> Known hereditary CRC syndromes, caused by heritable highly penetrant single-gene mutations, account for approximately 5% of all CRC cases.<sup>3</sup> These syndromes, each of which has its characteristic features, include Lynch syndrome (2 to 4%), familial adenomatous polyposis (1%), *MUTYH*-associated polyposis (less than 1%) and hamartomatous polyposis syndromes (less than 0.1%) such as juvenile polyposis syndrome and Peutz-Jeghers syndrome.

This article will focus on the currently known hereditary CRC syndromes. A glossary of some terms used is provided in Box 1.

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## THE ADENOMA-CARCINOMA SEQUENCE

CRC is usually preceded by adenomatous polyps, which originate from the glandular tissue of the bowel and may become malignant if not removed. In sporadic CRC, the transformation from adenoma to carcinoma usually takes a number of years; in contrast, the adenoma–carcinoma sequence associated with some hereditary CRC syndromes, such as Lynch syndrome, evolves more rapidly.<sup>4</sup> Surveillance colonoscopy with removal of polyps has been shown to be effective in preventing CRC and reducing CRC mortality.<sup>5</sup>

Hamartomatous polyps are composed of the normal cellular elements of the gastrointestinal tract but have a disorganised architecture. They grow along with, and at the same rate as, the host tissue. The cancer pathogenesis associated with hamartomatous polyposis syndromes is not fully defined. It has been postulated to involve malignant transformation occurring within co-existing adenomatous polyps, hamartomatous polyps undergoing adenomatous followed by carcinomatous transformation or, possibly, direct transformation from hamartomas to carcinomas.<sup>6</sup>

## TUMOUR PREDISPOSITION: THE KNUDSON 'TWO-HIT' HYPOTHESIS

Alfred Knudson's 'two-hit' hypothesis describes the tumour predisposition associated with most hereditary cancer syndromes. The hypothesis proposes that hereditary cancer is conferred by a germline mutation (representing the first hit) affecting one allele of a gene in every cell, with tumour developing only after the other allele of the gene is mutated (the second hit), the latter being a somatic change triggered by environmental and/or other genetic factors.

The genes in which germline mutations lead to tumour formation can be broadly categorised into:

- tumour suppressor genes with loss of function mutations (e.g. *APC* gene associated with familial adenomatous polyposis; *STK11* gene associated with Peutz-Jeghers syndrome)
- genes involved in DNA repair (e.g. mismatch repair genes associated with Lynch syndrome and *MUTYH*-associated polyposis)

## 1. HEREDITARY COLORECTAL CANCER: GLOSSARY

- **Allele.** One version of a gene at a given location (locus) along a chromosome.
- **Biallelic mutations.** Mutations, either compound heterozygous (nonidentical) or homozygous (identical), that are present in both copies of a gene; usually required for expression of an autosomal recessive disorder.
- **De novo mutation.** An alteration in a gene that occurs for the first time in a family member, as a result of a spontaneous mutation occurring around the time of conception of this individual.
- **Exome.** The part of the genome formed by exons. Exons are joined together after RNA splicing and removal of introns to form mature mRNA prior to protein translation.
- **Familial.** A phenotype that occurs in more than one family member; may have genetic or nongenetic aetiology. Nongenetic aetiology includes shared environmental or lifestyle factors.
- **Germline mutation.** A gene mutation that can be passed to subsequent generations through germ (ova/sperm) cells. When inherited, such mutation is present in virtually every cell, including germ cells. In contrast, somatic mutations arise later in life in the tissue cells of an individual and cannot be passed on to offspring.
- **Microsatellite instability (MSI).** MSI is characterised by abnormal expansion or contraction of simple repetitive DNA sequences (i.e. microsatellite repeats) that are ubiquitously present throughout the genome. MSI in colorectal cancer indicates a defect in one of the mismatch repair genes caused by either somatic changes or a germline defect.
- **Penetrance.** The proportion of individuals with a gene mutation known to cause a disease who develop the associated phenotype. 'Complete' penetrance means that almost all individuals with a disease-causing mutation will invariably develop symptoms and signs of the disease; 'incomplete' or 'reduced' penetrance means that not everyone with a disease-causing mutation will develop the associated phenotype.
- **Pre-implantation genetic diagnosis (PGD).** An intervention to achieve a pregnancy unaffected by a genetic disorder, via in vitro fertilisation (IVF), and with the added step of screening the embryos for the family mutation so that only unaffected embryos are transferred back into the mother's uterus for the pregnancy to continue. This intervention requires prior identification of the family mutation accounting for the genetic disorder.
- **Sporadic.** Occurrence of a disorder caused by nongenetic factors.

- genes involved in critical cellular pathways such as the transforming growth factor-beta (TGF-beta) pathway (e.g. *BMPRIA*/*SMAD4* genes associated with juvenile polyposis syndrome).

## HOW ARE HEREDITARY CRC SYNDROMES DIAGNOSED?

Each of the hereditary CRC syndromes has its own distinctive constellation of clinical features allowing its recognition and diagnosis, as summarised in the Table and flowchart.

Establishing a clinical diagnosis, by ascertaining a family history of related tumours (e.g. multiple affected close relatives on the same side of family with same/related malignancies

**TABLE. SUMMARY OF MAJOR COLORECTAL CANCER PREDISPOSITION SYNDROMES**

Syndrome	% CRC cases	Associated gene(s)	Key features	Risk management <sup>7</sup>
<b>Nonpolyposis</b>				
Lynch syndrome (LS)	2–4%	Mismatch repair (MMR) genes: <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i>	<ul style="list-style-type: none"> <li>No/few polyps</li> <li>MMR deficient and/or microsatellite unstable tumours</li> <li>Risk of other malignancies: endometrial (up to 60% lifetime risk); less frequently ovarian, gastric, small bowel, hepatobiliary, urothelial, brain and sebaceous tumours</li> </ul>	<ul style="list-style-type: none"> <li>Annual colonoscopy from age 25 years</li> <li>Consider biennial gastroscopy from age 30 years in families with gastric cancer or those at high ethnic risk</li> <li>Risk-reducing hysterectomy and bilateral salpingo-oophorectomy by age 40 years</li> </ul>
<b>Adenomatous polyposis</b>				
Familial adenomatous polyposis (FAP)	1%	<i>APC</i>	<ul style="list-style-type: none"> <li>Hundreds to thousands of adenomatous polyps</li> <li>Young onset polyps/CRC</li> <li>Variable features: polyps of gastric fundus, duodenum or small bowel, duodenal carcinoma, desmoid tumours, osteomas, congenital hypertrophy of retinal pigment epithelium</li> </ul>	<ul style="list-style-type: none"> <li>Annual or biennial sigmoidoscopy/colonoscopy from age 12 to 15 years, then annual colonoscopy at onset of polyps</li> <li>Prophylactic colectomy when polyp burden high, usually by late teens</li> <li>Upper GI endoscopy from age 25 years</li> </ul>
<i>MUTYH</i> -associated polyposis (MAP)	<1%	<i>MUTYH</i>	<ul style="list-style-type: none"> <li>Autosomal recessive inheritance</li> <li>Attenuated polyposis phenotype (polyp count range, 1 to 100)</li> <li>Variable features: duodenal/gastric fundic polyps, extraintestinal tumours</li> </ul>	<ul style="list-style-type: none"> <li>Colonoscopy from age 20 years, biennially if no polyps detected, annually when polyps detected until colectomy is indicated</li> <li>Upper GI endoscopy from age 25 years</li> </ul>
<b>Serrated polyposis</b>				
Serrated polyposis syndrome (SPS)	Unknown	Unknown	<ul style="list-style-type: none"> <li>Polyps are frequently small and flat, making endoscopic detection difficult</li> <li>Co-occurrence of adenomatous polyps is common</li> <li>Aetiology unknown, inherited component implicated although inheritance pattern not clear</li> <li>Genetic testing not available</li> </ul>	<ul style="list-style-type: none"> <li>Patients with SPS: colonoscopy every 1 to 3 years depending on polyp number and size</li> <li>Unaffected FDR (without polyps) of patients with SPS: consider colonoscopy every 3 to 5 years from age 40 years or 10 years younger than youngest age at diagnosis of SPS-related CRC</li> </ul>

at younger ages) as well as a personal history (e.g. polyp count/histology and presence of extracolonic manifestations), is essential prior to considering genetic testing (Box 2; Figures 1a to c and Figures 2a to d). A family history may not always be present, as the patient may be the first to be affected in the family (caused by a *de novo* mutation). The lack of family history may also be due to small family size, premature death or incomplete penetrance.

### HOW DOES GENETIC TESTING WORK? Mutation search

If a clinical diagnosis of hereditary CRC is suspected, the index case should be referred to a familial cancer clinic for assessment, genetic counselling prior to testing if indicated, and risk management, bearing in mind that diagnostic genetic testing is only warranted in a minority of patients. This initial step in molecular diagnosis, called 'mutation search', involves taking a blood sample from an affected family

member (the index case) and searching for mutations in targeted genes. This may take some months.

At present, molecular genetic testing in its traditional sense is limited by its ability to find causative gene mutations because in many cases more than one gene may be implicated and/or the disease may be caused by mutations in an unknown gene/genes. Testing is, therefore, only beneficial for those families meeting stringent clinical diagnostic criteria.

**TABLE. SUMMARY OF MAJOR COLORECTAL CANCER PREDISPOSITION SYNDROMES CONTINUED**

Syndrome	% CRC cases	Associated gene(s)	Key features	Risk management <sup>7</sup>
<b>Hamartomatous polyposis</b>				
Juvenile polyposis syndrome (JPS)	<0.1%	<i>BMPR1A</i> , <i>SMAD4</i> (each accounting for 20% of JPS cases)	<ul style="list-style-type: none"> <li>• ‘Juvenile’ refers to a particular type of hamartomatous polyp</li> <li>• Mostly benign, malignant transformation may occur</li> <li>• May cause bleeding, protein-losing enteropathy</li> <li>• Cases due to <i>SMAD4</i> mutation may present with combined JPS and hereditary haemorrhagic telangiectasia</li> </ul>	<ul style="list-style-type: none"> <li>• Before polyps develop: biennial colonoscopy (from age 15 years) and upper GI endoscopy (from age 25 years)</li> <li>• Annual surveillance if polyps present</li> <li>• Consider prophylactic colectomy if high polyp burden</li> <li>• Hereditary haemorrhagic telangiectasia evaluation in those with <i>SMAD4</i> mutation</li> </ul>
Peutz-Jeghers syndrome (PJS)	<0.1%	<i>STK11</i>	<ul style="list-style-type: none"> <li>• PJS-type hamartomatous polyps in small bowel and/or elsewhere</li> <li>• Characteristic mucocutaneous pigmentation</li> <li>• Major morbidity in children relates to intestinal intussusception</li> <li>• Risk of adult-onset cancers: breast, gynaecological, pancreatic</li> </ul>	<ul style="list-style-type: none"> <li>• GI surveillance from age 10 years, for detection and removal of polyps to prevent complications: annual haemoglobin; video capsule endoscopy or magnetic resonance endoscopy at least every 3 years; upper GI endoscopy and colonoscopy at least every 3 years</li> <li>• Above GI screening to continue through adulthood for cancer surveillance</li> <li>• Breast cancer screening from age 30 years</li> <li>• Pap smear and pelvic examination from age 18 years</li> </ul>

ABBREVIATIONS: CRC = colorectal cancer; FDR = first-degree relative; GI = gastrointestinal; MMR = mismatch repair.

### Predictive genetic testing

Once a causative gene mutation is identified in an index case, his or her close relatives can then be offered ‘predictive’ genetic testing to determine whether or not they have the family gene mutation. This takes several weeks. Predictive genetic testing can definitively determine which family members are at higher cancer risk and thus would benefit from risk management. It can also determine those who do not have the family gene mutation, in which case they are at average cancer risk and can be spared unnecessary screening and concern.

Furthermore, once a causative gene mutation is identified in the family, it opens up reproductive options such as pre-implantation genetic diagnosis (PGD).

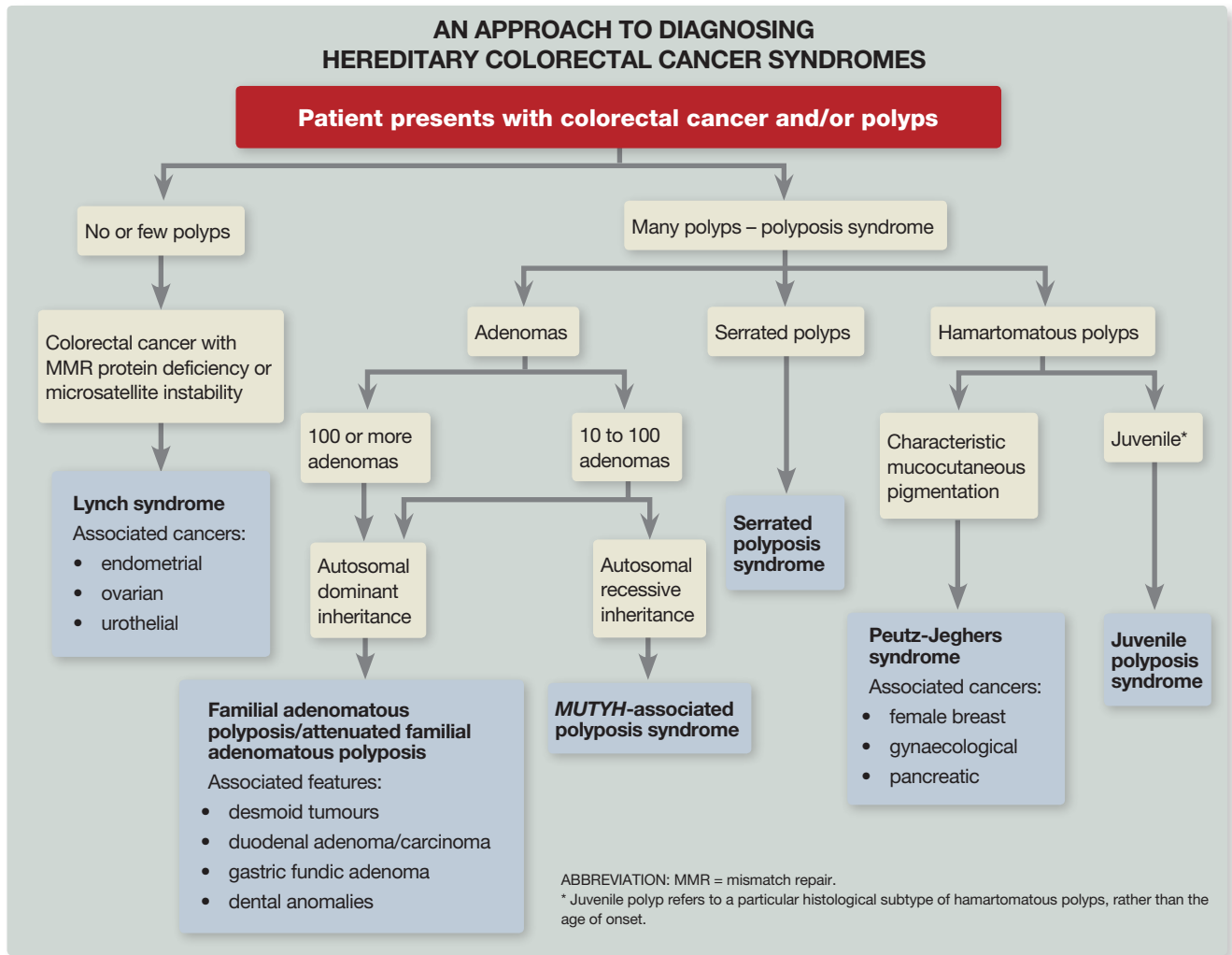
### Funding and the future

In Australia, Medicare and private health insurance do not fund genetic testing for most hereditary cancer syndromes. If testing is deemed warranted as assessed by a familial cancer clinic, publicly funded testing is available through the clinic budgeted by the state and territory health departments. Self-funded testing is possible and can be facilitated by the clinic, with important pre- and post-test counselling provided. The cost of testing varies depending on the gene involved and the technology used, but ranges from a few hundred to a few thousand dollars.

As with the trend worldwide, familial cancer clinics across Australia are moving towards the use of next-generation sequencing (NGS) technology as a diagnostic tool.

Unlike traditional Sanger sequencing (testing single genes at a time), NGS has the capacity of simultaneously analysing tens of thousands of genes. NGS technology has led to the discovery of new CRC-predisposition genes through whole-genome or whole-exome sequencing (e.g. *POLE* and *POLD1* genes, which encode DNA polymerase enzymes important in DNA replication and repair, with mutation phenotype yet to be fully characterised).<sup>8</sup> NGS has also enabled the use of multiplex panels for simultaneous sequencing of multiple known CRC susceptibility genes in individual patients.<sup>9,10</sup>

Concerns regarding the use of NGS include bioinformatic challenges, data interpretation and the potential return of incidental findings.<sup>11</sup> Despite these, it is



anticipated that NGS-based testing will be widely used in clinical practice in the near future, driven partly by the lower cost of NGS-based testing compared with the traditional targeted strategy involving Sanger sequencing.

**WHY DIAGNOSE HEREDITARY CRC SYNDROMES?**

Recognising hereditary CRC syndromes is important because these syndromes constitute a group where molecular diagnosis, identification of unaffected at-risk family members via predictive genetic testing, and implementation of early screening at more frequent intervals would prevent CRC and reduce CRC mortality. In addition, the management of the index patient may be different if the underlying diagnosis is known. For example, a diagnosis of Lynch syndrome means that surveillance colonoscopy should

be performed annually, rather than dictated by the number of polyps found. Moreover, many of these hereditary CRC syndromes are associated with predisposition to extracolonic tumours, and diagnosis allows effective risk-reducing strategies to be undertaken appropriately, thus reducing overall cancer incidence.

The website *eviQ Cancer Treatments Online*, developed by Cancer Institute NSW, is an online resource for national guidelines on referral, genetic testing and risk management for various cancer genetic syndromes, including hereditary CRC syndromes (<http://www.eviq.org.au>).<sup>12</sup> It is widely used by familial cancer clinics across Australia, as well as by other health professionals.

**HEREDITARY CRC SYNDROMES**

**Lynch syndrome**

Lynch syndrome (LS), previously known

as hereditary nonpolyposis colon cancer, is the most common form of hereditary CRC, accounting for 2 to 4% of incident CRC, and has a population incidence of 1 in 440.<sup>3,13</sup> It is characterised by inherited predisposition to CRC, often with younger ages of onset (up to 80% lifetime risk, mean age at diagnosis ranging from 44 to 61 years), as well as endometrial cancer (up to 60% lifetime risk) and, less frequently, cancers of the ovary, stomach, small bowel, hepatobiliary tract and urinary tract as well as brain (Turcot variant) and sebaceous tumours (Muir-Torre variant).<sup>14</sup>

LS is an autosomal dominant condition caused by a germline mutation in one of the mismatch repair (MMR) genes, namely *MLH1*, *MSH2*, *MSH6* or *PMS2*. The MMR genes encode the MMR proteins, which play an important role in error-proofing during DNA replication.<sup>15</sup> LS-associated tumours

## 2. PERSONAL AND FAMILY HISTORY CHARACTERISTICS SUGGESTIVE OF A HEREDITARY COLORECTAL CANCER SYNDROME

### Personal history

- Age of onset (typically <50 years)
- High number of polyps
- More than one primary cancer (synchronous or metachronous CRC; other associated cancers)
- Presence of rare tumours (e.g. sebaceous tumours)
- Presence of extracolonic features (e.g. desmoid tumours)
- Tumour testing (e.g. MMR protein-deficient CRC)

### Family history

- Number of affected relatives (typically three or more) on the same side of family
- Closeness of affected relatives (first- or second-degree)
- Presence of related tumours (e.g. CRC and endometrial cancers)
- Young age of onset of tumours

ABBREVIATIONS: CRC = colorectal cancer; MMR = mismatch repair.

are deficient in the MMR protein (MMR-deficient), thereby displaying immunohistochemical loss of relevant MMR proteins and microsatellite instability (MSI).<sup>16</sup> The lifetime cancer risks associated with LS vary according to the specific MMR gene involved.<sup>17</sup>

Historically, the diagnosis of LS was suspected based on clinical criteria, namely the Amsterdam I/II criteria and/or the (revised) Bethesda guidelines (Box 3).<sup>18,19</sup> However, tumour testing is now widely utilised (immunohistochemistry and/or MSI testing) and this has high sensitivity and specificity for LS.<sup>20</sup> Furthermore, the lack of a specific MMR protein via immunohistochemistry can also direct germline testing of that specific gene. More recently, population-based screening for LS (universal screening of all incident CRC for MMR deficiency and subsequent referral for consideration of germline genetic



Figures 1a to c. Endoscopic appearances of different gastrointestinal polyps. a (left). Conventional adenoma, attached to the bowel mucosa via a stalk. b (centre). Numerous polyps seen in a patient with familial adenomatous polyposis. c (right). Sessile polyp, showing the flattened and broad-based appearance, making its detection difficult.

FIGURES 1A AND 1C REPRODUCED COURTESY OF PROFESSOR MICHAEL BOURKE, SYDNEY, NSW.

testing) has been shown to be potentially effective.<sup>21</sup> Some centres in Australia have adopted universal screening.

It should be noted that approximately 12% of sporadic CRCs display MSI and/or are MLH1-deficient on immunohistochemistry.<sup>22</sup> This occurs as a result of somatic *MLH1* hypermethylation, rather than an *MLH1* germline mutation.<sup>23</sup> In CRCs displaying MSI or MLH1 deficiency, especially in those patients diagnosed at relatively older ages, *BRAF* tumour testing may help distinguish between sporadic cases (*BRAF* mutation present) and those associated with LS (*BRAF*-wild type), as somatic *BRAF* mutations are associated with sporadic CRCs that develop through the methylation pathway.<sup>24,25</sup>

### Risk management

Identifying individuals with LS is important because colonoscopic surveillance reduces CRC mortality and prophylactic surgery substantially reduces the risk of gynaecological cancers in both index cases and at-risk relatives.<sup>26-28</sup> According to eviQ risk management guidelines, annual colonoscopy is recommended in individuals with LS from the age of 25 years, and second-yearly gastroscopy should be considered from the age of 30 years for those with a family history of gastric cancer or who are at high ethnic risk (e.g. Chinese, Korean, Chilean and

Japanese).<sup>7</sup> Currently there is insufficient evidence to routinely recommend risk-reducing medication, such as aspirin.

Risk-reducing hysterectomy and bilateral salpingo-oophorectomy are recommended when childbearing is complete or by age 40 years, as there is no effective screening for endometrial or ovarian cancers. It is recommended that patients be referred to experienced hands such as a gynaecological oncologist for such risk-reducing surgeries.

### Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is a colon cancer predisposition syndrome characterised by the development of hundreds to thousands of precancerous colonic adenomatous polyps, with a mean age of polyp onset of 16 years (range 7 to 36 years) and a more than 95% lifetime CRC risk in untreated individuals (Figures 1b and 2a).<sup>29</sup> It accounts for 1% of CRC.<sup>30</sup> Variable extracolonic manifestations include those that are potentially life-threatening, such as duodenal adenomas/carcinomas and desmoid tumours, as well as those that are clinically benign, such as gastric fundic polyps, osteomas, congenital hypertrophy of the retinal pigment epithelium and dental anomalies.

Attenuated FAP (aFAP) is characterised by the presence of fewer colonic polyps (average 30, and more proximally located)

and/or polyps occurring at an older age compared with classic FAP, and usually there are no extracolonic manifestations.

FAP and aFAP are autosomal dominant conditions caused by a germline mutation in the *APC* gene. This tumour suppressor gene encodes adenomatous polyposis coli (APC) protein, which plays a critical role in many cellular processes. Gardner and Turcot syndromes historically refer to the association of colonic polyposis typical of FAP and osteomas/soft tissue tumours or central nervous system tumours, respectively, prior to the identification of the *APC* gene.

Testing for FAP should be considered for individuals with multiple colonic polyps, especially in, but not limited to, those with a family history consistent with an autosomal dominant inheritance. In the past, before the availability of genetic testing, all at-risk relatives (e.g. siblings and children of those with clinical FAP) had to be screened annually for polyps from age 12 years. Now, for most families, a causative gene mutation can be found with 'mutation search' in the index case, then 'at-risk' relatives can be tested in the early teenage years to determine their need for bowel screening.

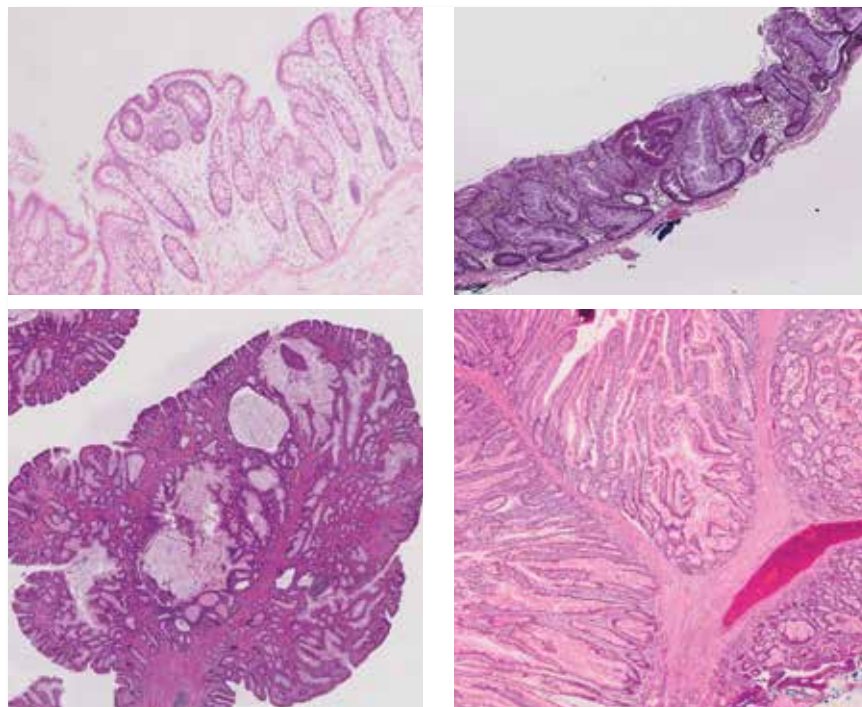
#### Risk management

For patients with FAP and their relatives identified to have the family *APC* gene mutation, screening (with annual or biennial sigmoidoscopy/colonoscopy from age 12 to 15 years, and then annual colonoscopy once polyps start developing) and ultimately prophylactic colectomy (which is standard of care once polyp burden is high, usually by the late teens) results in a significant reduction in CRC diagnosis.<sup>7,31</sup>

Annual surveillance of residual rectum or ileal pouch is required following colectomy. Upper gastrointestinal endoscopy is recommended from the age of 25 years, with frequency dependent on the findings.<sup>7</sup> There is no evidence to routinely recommend surveillance for extraintestinal tumours.

#### **MUTYH-associated polyposis**

*MUTYH*-associated polyposis (MAP) is an autosomal recessive condition caused



Figures 2a to d. Histological features (haematoxylin-eosin stain) of different gastrointestinal polyps. a (top left). Colonic microtubular adenoma from a patient with familial adenomatous polyposis, showing mild cytological dysplasia involving superficial portion of only a few adjacent crypts. b (top right). Colonic sessile serrated adenoma showing extension of the serrations to the crypt base with dilated inverted T- or L-shaped crypts, reflecting disordered proliferation. c (bottom left). Juvenile polyp of colon typically displaying mucus-filled dilated crypts, expanded lamina propria with inflammatory infiltrate and, unlike Peutz-Jeghers-type hamartomatous polyps, absence of smooth muscle proliferation. d (bottom right). Intestinal Peutz-Jeghers syndrome polyp showing characteristic arborising pattern of smooth muscle proliferation.

FIGURES 2A TO D REPRODUCED COURTESY OF DR DUNCAN MCLEOD, SYDNEY, NSW.

by biallelic mutations in the *MUTYH* gene. This gene encodes the protein mutY homologue (MYH) glycosylase, which is involved in DNA base excision repair.

Patients with MAP exhibit an attenuated polyposis phenotype (mean polyp count, 50; range, one to 100), with a lifetime CRC risk of 85% without treatment.<sup>32,33</sup> MAP accounts for approximately less than 1% of all CRC cases.<sup>32,34</sup> Other features variably associated with MAP include duodenal/gastric fundic polyps and extraintestinal neoplasias.<sup>35</sup>

For patients with 10 or more colorectal adenomas, especially if no germline *APC* mutation has been identified and the family history is compatible with recessive inheritance, genetic testing of *MUTYH* may be indicated.

#### Risk management

Clinical care of patients and their relatives with MAP is similar to that of those with familial adenomatous polyposis. Colonoscopy is recommended from age 20 years, on a biennial basis if no polyps are detected, and annually when polyps are detected, until colectomy is indicated. Upper gastrointestinal endoscopy is recommended from the age of 25 years.<sup>7</sup>

#### **Serrated polyposis syndrome**

Previously known as hyperplastic polyposis (HP), serrated polyposis syndrome (SPS) is a syndrome of unknown genetic basis characterised by the development of multiple 'serrated' polyps in the colorectum and associated with an increased CRC risk.<sup>36</sup> These polyps have characteristic macro- and

### 3. CLINICAL CRITERIA FOR IDENTIFICATION OF PATIENTS WITH SUSPECTED LYNCH SYNDROME

#### Amsterdam II criteria<sup>18</sup>

The fulfilment of *all* the criteria listed below identifies patients with LS, with a sensitivity of 22% (range 13 to 67%) and a specificity of 98% (range 97 to 100%)<sup>17</sup>

- Three or more relatives with confirmed LS-associated cancer\*, one of whom is a first-degree relative of the other two
- Two or more successive generations affected with LS-associated cancer
- One or more LS-associated cancer diagnosed before age 50 years
- Familial adenomatous polyposis is excluded

#### Revised Bethesda guidelines<sup>19</sup>

These guidelines identify CRC cases where tumour testing is indicated. The fulfilment of *any* of the criteria listed below has a sensitivity of 82% (range 78 to 91%) and a specificity of 77% (range 75 to 79%) for LS<sup>17</sup>

- CRC diagnosed before age 50 years
- Presence of synchronous or metachronous LS-associated cancers\*
- CRC diagnosed before age 60 years with pathology features suggestive of high-level microsatellite instability<sup>†</sup>
- Patient with CRC and at least one first-degree relative with a LS-associated cancer diagnosed before age 50 years
- Patient with CRC and at least two first- or second-degree relatives diagnosed with a LS-associated cancer at any age

ABBREVIATIONS: CRC = colorectal cancer; LS = Lynch syndrome.

\* LS-associated cancers include colorectal, endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract and brain cancers, and sebaceous gland carcinomas/adenomas.

<sup>†</sup> Pathology features suggestive of high-level microsatellite instability include Crohn's-like lymphocytic infiltration, mucinous/signet cell differentiation and/or medullary growth pattern.

microscopic appearances (flattened and broad-based endoscopically, referred to as sessile; and a saw tooth appearance under the microscope, referred to as serrated) (Figures 1c and 2b). Co-occurrence of conventional adenomas in the large intestine is common.<sup>36</sup>

Up to 40% of patients with SPS have a family history of CRC, and occasionally SPS may occur in more than one family member, implicating an inherited component.<sup>37</sup> However, no associated genes have been identified, so no genetic testing is available.

A clinical diagnosis of SPS is made based on the WHO diagnostic criteria:<sup>38</sup>

- at least five serrated polyps proximal to the sigmoid colon, with two or more polyps being more than 10 mm, or
- more than 20 serrated polyps of any size distributed throughout the colon, or
- any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS.

#### Risk management

In patients with SPS, colonoscopy is recommended every one to three years depending on the number and size of polyps.<sup>7</sup> In unaffected individuals (without polyps) who have a first-degree relative with SPS, the risk of CRC is unclear but it is reasonable to consider colonoscopy every three to five years from the age of 40 years or from 10 years younger than the age at diagnosis of the youngest person with CRC related to SPS in the family.<sup>39,40</sup>

#### Juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant predisposition to multiple hamartomatous gastrointestinal polyps with age of onset often before 20 years.<sup>41</sup> The term 'juvenile' refers to the type of polyps, which are hamartomas with a distinct histology differing from that of adenomas, rather than to the age of onset. Histologically, juvenile polyps display mucus-filled dilated glands, inflammatory infiltrate and, unlike Peutz-Jeghers

syndrome-type hamartomatous polyps, absence of smooth muscle proliferation (Figure 2c).<sup>42</sup> Most juvenile polyps are benign, but they may cause bleeding, anaemia and/or protein-losing enteropathy. Malignant transformation can occur, with an associated lifetime CRC risk of 30 to 40%, and to a lesser degree upper gastrointestinal cancers.<sup>43-45</sup>

It should be noted that solitary colorectal juvenile polyps occur in approximately 2% of children. These polyps are sporadic and are not known to be associated with an increased risk of gastrointestinal cancer.<sup>46</sup>

Two genes known to be associated with JPS are *BMPRIA* and *SMAD4*, each accounting for approximately 20% of JPS cases.<sup>47</sup> These genes encode bone morphogenetic protein receptor type 1A and SMAD family member 4 protein, respectively, both of which are involved in the transforming growth factor-beta (TGF-beta) signalling pathway that, in turn, modulates many important cellular processes, including proliferation and differentiation.<sup>48</sup> The genetic aetiology of the remaining 60% of clinical JPS cases is unknown. Approximately 20% of individuals with a *SMAD4* mutation may present with a combined syndrome of JPS and hereditary haemorrhagic telangiectasia,<sup>49</sup> the latter being a generalised vascular malformation disorder.

Genetic testing for the two known genes is available if the patient fulfils the following clinical diagnostic criteria:<sup>42</sup>

- more than five juvenile polyps of the colorectum, or
- multiple juvenile polyps throughout the gastrointestinal tract, or
- any number of juvenile polyps and a family history of JPS.

#### Risk management

Colonoscopy and upper endoscopy are recommended for patients with JPS and at-risk relatives, on a biennial basis from the ages of 15 years and 25 years, respectively, before polyps develop; and annually if polyps are present.<sup>7</sup> Prophylactic colectomy can be considered if polyp burden is high. Additionally, all patients with JPS





Figure 3. Characteristic mucocutaneous pigmentation associated with Peutz-Jeghers syndrome. This can occur around the mouth, eyes and nostrils, on the fingers and buccal mucosa and in the perianal area, and is most pronounced in early childhood and may fade in puberty/adulthood.

caused by a *SMAD4* mutation should be evaluated for the symptoms and signs of hereditary haemorrhagic telangiectasia, including pulmonary and cerebral arteriovenous malformations.

### Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition characterised by gastrointestinal hamartomatous polyposis, mucocutaneous pigmentation and cancer predisposition (Figure 3). The PJS-type hamartomatous polyps are usually benign and occur most commonly in the small intestine, although they can occur anywhere within, and rarely outside, the gastrointestinal tract.<sup>50,51</sup> The age of polyp onset is variable, mostly in the mid-teenage years but can be as early as the first few years of life. The polyps may cause complications such as bowel obstruction, intussusception, bleeding and/or anaemia.<sup>51</sup> Affected individuals are at increased risk for a wide variety of malignancies (which are usually of adult onset), including gastrointestinal (up to 57% lifetime risk), female breast, gynaecological and pancreatic cancers.<sup>52</sup>

The diagnosis of PJS is based on clinical findings:<sup>53</sup>

- two or more histologically confirmed PJS-type hamartomatous polyps,

typically displaying an arborising pattern of smooth muscle proliferation (Figure 2d), or<sup>54</sup>

- any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation (Figure 3), or
- any number of PJS-type polyps in one individual who has a family history of PJS in a close relative(s), or
- characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative(s).

The majority of patients with clinical PJS have a germline mutation in the *STK11* gene, which is a tumour suppressor gene encoding the serine/threonine kinase 11 protein.

### Risk management

Gastrointestinal surveillance is recommended to start from age 10 years, with annual haemoglobin levels together with video capsule endoscopy or magnetic resonance endoscopy, as well as upper endoscopy and colonoscopy, at least every three years.<sup>7</sup> Screening at such a young age is aimed at reducing morbidities associated with intussusception, which is a major complication that invariably leads to surgical resection of large segments of intestine, and can be prevented by timely detection and removal of polyps. At present, there is limited literature documenting the effectiveness of gastrointestinal cancer surveillance in PJS.<sup>52,55</sup> Nevertheless, expert opinion recommends that the above screening regime be continued through adulthood.<sup>7</sup>

Furthermore, breast cancer screening should start from age 30 years, with annual clinical examination and mammogram, as well as MRI if available. Bilateral risk-reducing mastectomy can be considered following counselling at a familial cancer clinic. Gynaecological surveillance is recommended from age 18 years with biennial Pap smear and pelvic examination.<sup>7</sup>

### CONCLUSION

Recognising hereditary CRC syndromes is important because effective risk-reducing

strategies are available to prevent associated cancers in both index patients and at-risk family members. Personal and family histories are essential in establishing a clinical diagnosis, and should be ascertained prior to considering genetic testing. Familial cancer clinics provide patients with information, support and guidance on decision-making for genetic testing, cancer risk management, and family/life planning.

Despite the promise offered by next generation sequencing as a diagnostic tool, determining family history and establishing an accurate clinical diagnosis remain crucial. As we enter the genomic era, it is anticipated that familial cancer clinics will play an even greater and more challenging role in interpreting complex genomic information that will be used to achieve both personalised cancer care and cancer prevention. **MT**

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A list of references is included in the website version ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)) and the iPad app version of this article.

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# Hereditary colorectal cancer

## What you need to know

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